CARBON MONOXIDE
A REVIEW
Dr. Domingo Aviado

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CARBON MONOXIDE

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Chapter 1

SUMMARY STATEMENTS ON THE INTERRELATIONSHIPS OF CIGARETTE SMOKE, CARBOXYHEMOGLOBIN, SMOKERS AND NONSMOKERS

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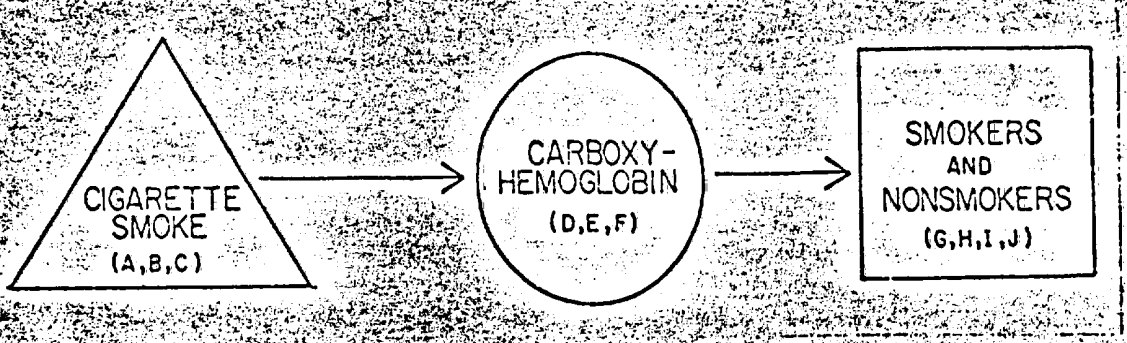

Since cigarette smoke contains carbon monoxide, it is suspected by some investigators that the carboxyhemoglobin level of smokers is elevated enough to adversely influence the cardiovascular system and central nervous system of smokers in general, to reduce the birth weight of infants and to cause respiratory symptoms in children of parents who smoke in particular. Even nonsmokers who are exposed to cigarette smoke are claimed to absorb carbon monoxide in sufficient amounts to be hazardous to their health.

The literature on the subject of cigarette smoke and carboxyhemoglobin is covered in this monograph to illustrate the invalid basis for the suspicion that smokers and nonsmokers suffer from the carbon monoxide contained in cigarette smoke. This general proposition is not supported by available facts which are summarized in ten statements, three relating to cigarette smoke (a, b, c), three to carboxyhemoglobin (d, e, f) and four to smokers and nonsmokers (g, h, i and j).

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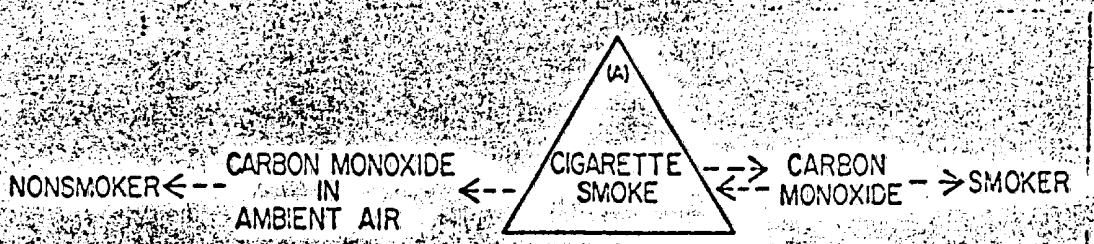

Summary Statement (a): A small and variable amount of carbon monoxide in cigarette smoke is absorbed by the smoker and even considerably less by the nonsmoker.

The total amount of carbon monoxide released from a burning cigarette varies from 5 to 80 ml, and the concentration in the cigarette smoke ranges from 0.5 to 8%. The 16-fold range in values is determined by the type of tobacco, speed of burning the cigarette and the amount of air diluting the smoke (see page 31). Of the amount of carbon monoxide inhaled with the cigarette smoke, about 54 to 87% is absorbed by the blood (see page 33).

It is difficult to estimate the amount of carbon monoxide that is inspired (mainstream smoke) separately from the amount that is not inhaled by the smoker (sidestream smoke). The quantity will depend on the amount and depth of inhalation and the frequency that the smoker inhales the mainstream smoke from the cigarette. Smokers vary in their smoking behavior, and an individual smoker has no set pattern of consuming cigarettes from hour to hour or from day to day. It is, therefore, misleading to attempt to quantitate the total amount of carbon monoxide that a smoker absorbs from cigarette smoke. The amount of carbon monoxide from cigarette smoke that is in the ambient air that a nonsmoker

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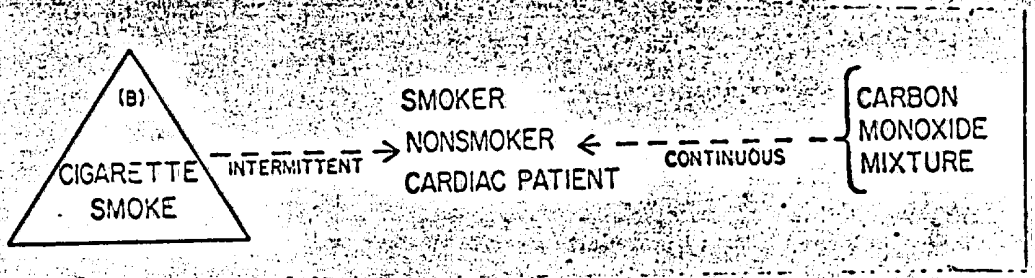
is likely to inhale is even more variable because of the prevailing movement of air in an enclosure (see page 203). Estimations based on nicotine concentration in the ambient air and on the amount of nicotine absorbed by the nonsmoker indicate that the nonsmoker absorbs less than 1/100th of the cigarette smoke absorbed by the smoker (see page 209).



Summary Statement (b): Almost all the reported health effects of low levels of carbon monoxide were determined by continuous administration of a fixed concentration of carbon monoxide which is not applicable to the smoking situation, characterized by intermittent exposure to carbon monoxide.

The available information on the effects of low levels of carbon monoxide on smokers and nonsmokers, with or without heart disease, is largely based on experimental inhalation of the gas, continuously for many hours a day or without interruption daily for several weeks. These experiments were designed to determine occupational standard indoors (see page 155) and air quality standard for outdoors (see page 195).

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The reported effects of inhalation of fixed concentrations of carbon monoxide on the cardiovascular system (see page 73) and the central nervous system (see page 104) do not necessarily apply to the intermittent exposure to carbon monoxide in the course of cigarette smoking. The theoretical analysis of the smoking

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situation postulating a gradual accumulation of carbon monoxide in the body in the course of smoking several cigarettes in a day[1] is not supported by three groups of observations in smokers. First: The carboxyhemoglobin level of smokers at the end of the day is about the same as at the start (see page 35). Second: Smokers with their preexisting level of carboxyhemoglobin absorb less carbon monoxide[2-4] than nonsmokers indicating that uptake of the gas is not only determined by the inhaled concentration but by a complex group of factors that cannot be predicted by theoretical equations. Third: In animal experiments, the effects on the blood are more severe with continuous fixed concentrations of exposure than with intermittent exposure even though the carboxyhemoglobin level at the end is the same.

The smoking subject cannot be simulated by intermittent inhalation of carbon monoxide in air mixture. There is evidence that the smoker consumes cigarettes in a self-regulatory manner, to keep nicotine and carboxyhemoglobin levels in the blood constant. It appears that the smoker controls the amount of smoke inhaled, subconsciously to derive a level of carboxyhemoglobin that is optimal for the individual. This aspect of self-regulation of carbon monoxide as well as the adaptation to it needs further investigation.

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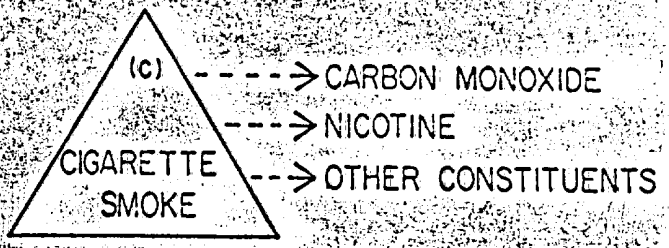

Summary Statement (c): Because of the presence in cigarette smoke of nicotine, which has pharmacologic actions opposite to those of carbon monoxide, the effects of carbon monoxide alone cannot be equated to cigarette smoking.

It is taken for granted by some reviewers that the inhalation of low levels of carbon monoxide elicits the same effects as cigarette smoking. The fallacy in this belief is that cigarette smoke contains nicotine, which can antagonize the effects of carbon monoxide on the heart (see page 68) and the central nervous system (see page 110). One form of interaction has been excluded, i.e. the potential of carbon monoxide to depress drug-metabolizing enzymes in the liver in general, and, in particular, the metabolizing enzymes for nicotine. There are experiments which show that low levels of carbon monoxide do not depress metabolizing enzymes.[5,6] The other constituents of cigarette smoke are not covered in this review because there is no information on their interaction with carbon monoxide. The possibility of interaction exists until appropriate experiments for exclusion are completed.

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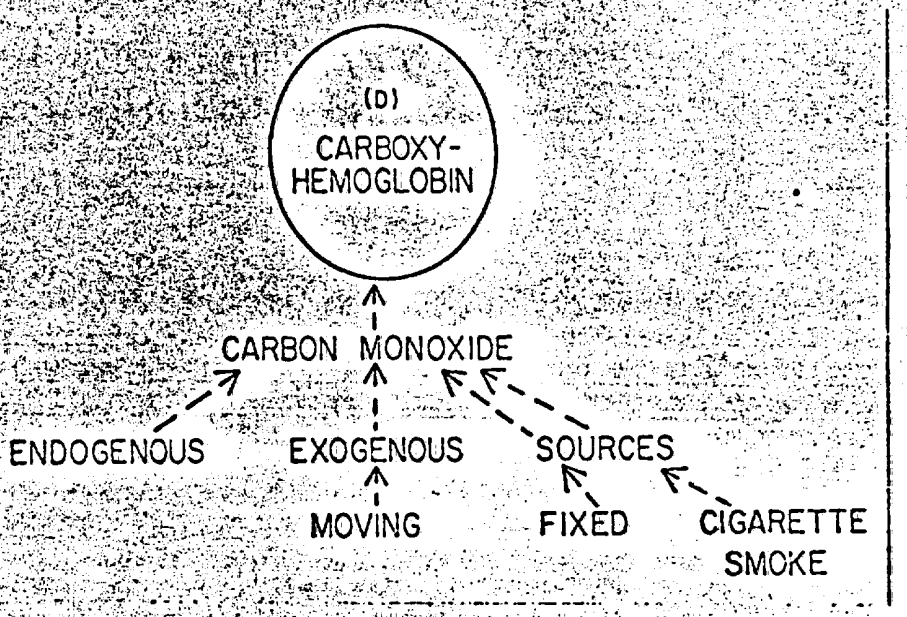

Summary Statement (d): The carboxyhemoglobin level in the blood of smokers represents not only carbon monoxide absorbed from cigarette smoke but also the carbon monoxide from exogenous sources and produced endogenously.

The uptake of carbon monoxide by the blood has been demonstrated during cigarette smoking (see page 33), inhalation of carbon monoxide mixtures in air (see page 104), exposure of workers to occupational sources of carbon monoxide (see page 148), exposure of workers and pedestrians to vehicular traffic (see page 165), and exposure to stationary or moving sources of carbon monoxide outdoors (see page 192) and indoors (see page 201). It is impossible to ascertain that a given amount of carboxyhemoglobin in the blood of smokers originates from cigarette smoke because the smoker is simultaneously exposed to other exogenous sources of carbon monoxide. Furthermore, there is an endogenous production of carbon monoxide which is represented by a variable fraction of the total carboxyhemoglobin in the blood of smokers and nonsmokers.[7,8] When nonsmokers and

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smokers are compared in terms of carboxyhemoglobin level, it is not to establish the effect of smoking. The comparison cannot exclude smokers with a high level of endogenous formation of carbon monoxide and nonsmokers with low level of endogenous formation. Different exogenous exposures of smokers and nonsmokers can further complicate the deriving of any conclusion with respect to the effect of smoking alone.

Nit picking

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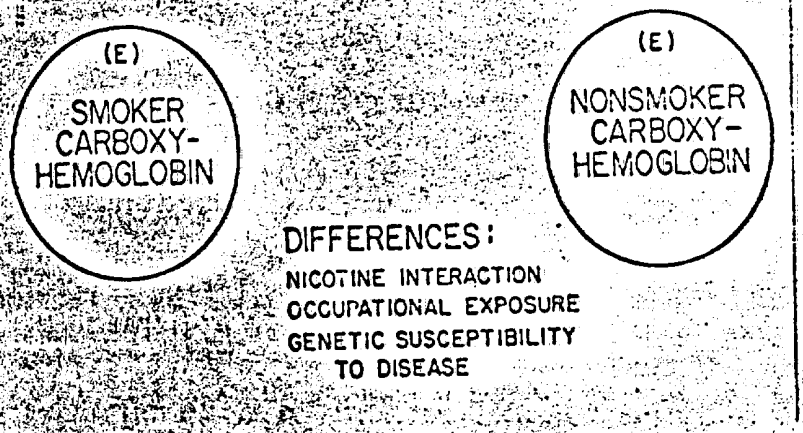

Summary Statement (e): The difference in carboxyhemoglobin levels between smokers and nonsmokers is accompanied by differences not only in cigarette use but also in occupational exposure and genetic susceptibility to disease.

Although the mean values for carboxyhemoglobin levels in the blood of smokers are higher than those for nonsmokers, there is a considerable overlapping in individual values. The standard deviation for the mean of smokers is considerably wider than that of nonsmokers in comparisons of blood donors (see page 25), anginal patients (see page 51), pregnant women (see page 128), welders (see page 150), motor vehicle drivers (see page 169) and pedestrians (see page 193). The practice of characterizing smokers by a single mean value has led to considerable confusion because of the variability in exposure to sources of carbon monoxide of smokers.

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The differences in the health of smokers and nonsmokers is explained usually by the smoking habit together with the difference in mean carboxyhemoglobin level. There are other factors that are difficult to exclude in accepting a causal relationship between smoking and elevated carboxyhemoglobin levels. First: Smokers

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adjust their consumption of cigarettes to maintain a constant level of nicotine,[9] as well as a constant level of carboxyhemoglobin; any effects of carbon monoxide are antagonized by nicotine because of their opposite actions on the heart and central nervous system (see Summary Statement c). Second: Smokers are more likely to be exposed to occupational-related hazards than nonsmokers, because there is a higher incidence of smokers employed in those hazardous jobs than in other groups.[10] The higher incidence of diseases among smokers may be a reflection of the higher incidence in exposure. Third: The metabolism of carbon monoxide and associated environmental pollutants is influenced by hereditary[11] and constitutional factors,[12,13] which may be different between smokers and nonsmokers. This possibility is difficult to prove or disprove but it has to be considered as a likely explanation for the difference in health characteristics between smokers and nonsmokers.

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(F)

CARBOXY-HEMOGLOBIN

ADAPTATION OF:

ERYTHROCYTES
BONE MARROW
LIVER
HEART
CENTRAL NERVOUS SYSTEM

Summary Statement (f): In the interpretation of results of prolonged exposure to low levels of carbon monoxide, the development of adaptation to carboxyhemoglobin by smokers should be considered.

Adaptation or acclimatization to low concentration of carbon monoxide is a phenomenon that has been ignored in the consideration of the health effects of carbon monoxide in cigarette smoke. That continuous exposure to carbon monoxide will lead to increase in tolerance in man and animals has been explained by adaptation of the erythrocytes, bone marrow, liver, heart and central nervous system.[14-19] Investigations planned in the future should be designed to determine the degree of adaptation, not only to carbon monoxide but also to nicotine contained in cigarette smoke.

Some adaptation probably does occur

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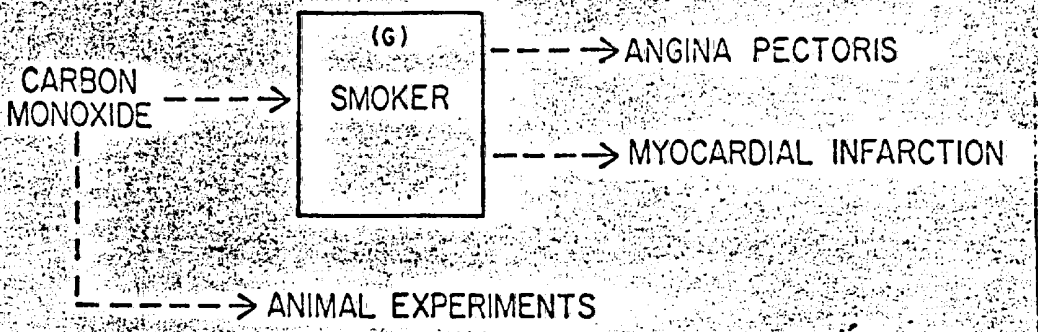

Summary Statement (g): The carboxyhemoglobin levels of cigarette smokers are not high enough to cause coronary heart disease.

The observations in patients with heart disease and in animals do not support the hypothesis that carboxyhemoglobin levels in cigarette smoke are high enough to provoke angina pectoris or cause myocardial infarction. The major shortcoming of the hypothesis is that the experimental procedure involves inhalation of carbon monoxide without nicotine. The nicotine in cigarette smoke produces cardiac actions opposite to those of carbon monoxide (see Chapter 3 beginning on page 46).

One topic not covered in Chapter 3 is the influence of carbon monoxide on the hemoglobin oxygen dissociation curve. The shift to the left with an elevation of carboxyhemoglobin means a decrease in oxygen release from the blood in the heart and tissues. It is important to point out that patients who develop heart disease have either a shift to the left or to the right and an abnormal hemoglobin is seen in patients with heart disease who are nonsmokers.[20-24] The appearance of an abnormal oxygen dissociation curve in smokers with heart disease cannot be caused by smoking alone since the same phenomenon is seen in patients who are nonsmokers.

Maybe

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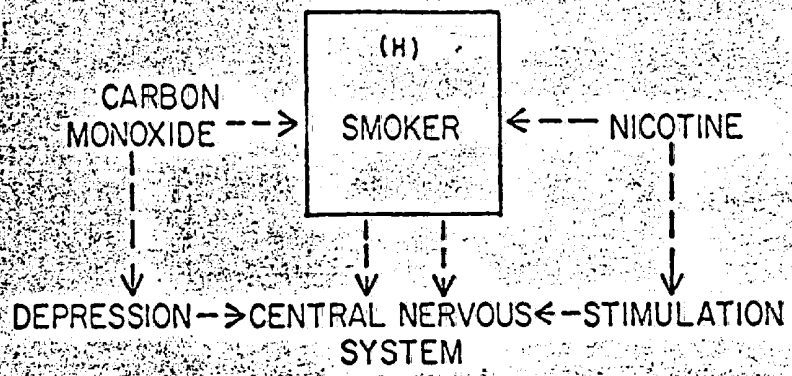

Summary Statement (h): It is unlikely that the carboxyhemoglobin levels of cigarette smokers are high enough to depress the central nervous system.

A review of the literature reveals that depression of the central nervous system by carbon monoxide is seen only when carboxyhemoglobin levels are above 20% saturation. The reports claiming a depression at levels below 20% are questionable and have not been confirmed. Since cigarette smokers rarely have a carboxyhemoglobin level reaching 20% saturation, a possible depressant influence of carbon monoxide on cerebral function can be excluded. Furthermore, nicotine absorbed by the smoker stimulates the central nervous system and can antagonize any depressant action of carbon monoxide (see Chapter 4 beginning on page 101).

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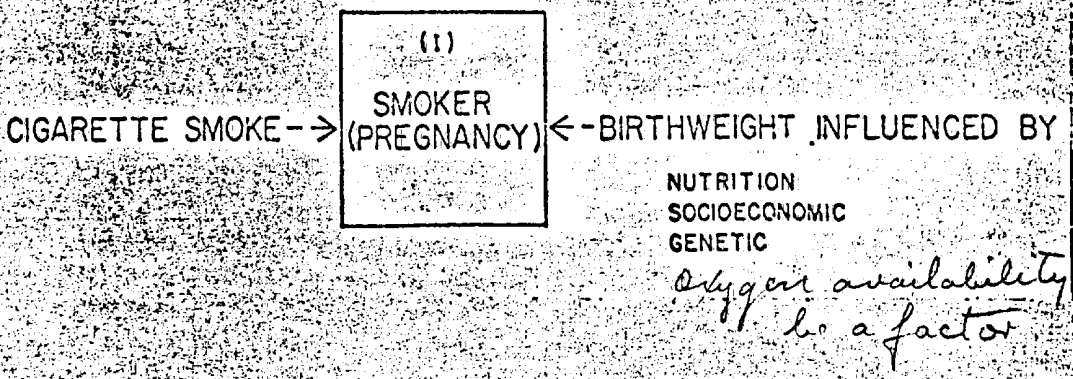

Summary Statement (i): The contention that smoking during pregnancy causes an elevation in carboxyhemoglobin level high enough to reduce birth weight of the newborn is not supported by experimental and epidemiologic data.

In the interpretation of epidemiologic data relating to smoking in pregnancy, the following factors contribute to the low birth weight of infants of smoking mothers: nutrition, socioeconomic factors and inherited genetic characteristics of the mother. The strength of these factors in influencing the birth weight of the newborn are discussed in detail in this monograph (see Chapter 5 beginning on page 126). The contention that carboxyhemoglobin levels of smoking mothers is a cause of low birth weight is discredited by the results of epidemiologic studies and experiments in animals exposed to cigarette smoke. Such experiments do not duplicate the results of exposure of pregnant animals to carbon monoxide.

Not all that convincing.

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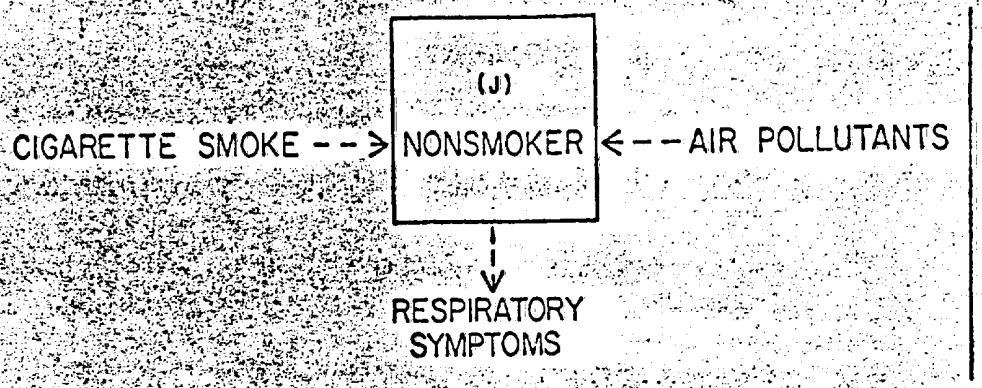

Summary Statement (j): There is no evidence that the health of a nonsmoker is threatened when exposed to cigarette smoke in an enclosed environment.

Actual measurements of carbon monoxide and nicotine levels indoors do not show concentrations approaching occupational exposure standards. Nonsmokers exposed in chambers or nonventilated rooms filled with cigarette smoke do not develop cardiovascular reaction or respiratory symptoms. Subjective complaints of nonsmokers are a psychosocial reaction to the irritation of the mucosa by chemical components of cigarette smoke other than carbon monoxide (see Chapter 9 beginning on page 201).

Yes

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Chapter 2

BLOOD CARBOXYHEMOGLOBIN LEVELS OF CIGARETTE SMOKERS AND NONSMOKERS

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Prior to the discussion of the possible health hazards of carbon monoxide contained in cigarette smoke, it is necessary to review the levels of carboxyhemoglobin in the blood of smokers. Measurements show a striking variability depending on the following: (a) the nature of the cigarette (presence of filter, porosity of the paper and type of tobacco); (b) frequency and depth of inhalation of the smoker; and (c) the carbon monoxide level in the immediate environment of the smoker. The last-mentioned factor represents the load or basic level of carbon monoxide in the ambient air that all persons are exposed to, smokers and otherwise. The overall exposure to occupational, residential and vehicular sources of carbon monoxide varies geographically.

It is possible to measure the amount of carbon monoxide in the ambient air and calculate the time-weighted levels of exposure in the course of a day. However, the quantitative expression of carboxyhemoglobin level in the blood is usually based on the analysis of a single sample. The carboxyhemoglobin level of a smoker fluctuates so much during the day that it is erroneous to regard the results of a single blood analysis as representative of a 24-hour level of carboxyhemoglobin. There is a transient elevation of carboxyhemoglobin immediately after smoking a cigarette but there is also a reduction during the nonsmoking interval. The rate of excretion of carbon monoxide is dependent on the physical activity of the smoker, another variable influencing carboxyhemoglobin level. The techniques for recording carboxyhemoglobin levels are

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more complex than that for carbon monoxide in the ambient air. Unless there is an improvement in technology, it is unlikely that a time-weighted value for carboxyhemoglobin in the blood of smokers will become available.

Almost all investigators use single measurements of carboxyhemoglobin as an approximation of the amount of carbon monoxide absorbed by cigarette smokers. Since the level is higher than that of nonsmokers, they conclude that the difference is due to the cigarette smoke. The inaccuracy in the comparison of carboxyhemoglobin levels of smokers and nonsmokers is discussed in this chapter.

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A. Carboxyhemoglobin Levels of Blood Donors

Blood donors have been used to compare the carboxyhemoglobin levels of smokers and nonsmokers. There is general agreement that the comparisons show higher levels of carboxyhemoglobin in smokers than in nonsmokers. However, it should be recognized that blood donors are selected individuals, some of them are professionals who derive part of their income in exchange for blood. The socioeconomic status of donors is different from those who do not engage in such an activity.

1. National Survey Conducted by Stewart et al.

From 1969 to 1972, Stewart and his collaborators conducted a survey of American blood donors for the purpose of determining the range of carboxyhemoglobin levels. Venous blood samples were obtained from 29,000 blood donors living in urban, suburban and rural communities in 18 metropolitan areas.[1-3] The carboxyhemoglobin saturation of blood donors in the various cities are tabulated on the next page.

The median carboxyhemoglobin saturation for the smokers is higher than that of nonsmokers. The magnitude of the differences between medians varies from city to city; the smallest difference is 2.0 (% saturation) for Houston; the largest is 4.4 for Los Angeles. It is unlikely that smokers smoke less in Houston than in Los Angeles. The difference in median levels for these cities reflects differences in the magnitude of exogenous sources of carbon monoxide.

a. Significance of carboxyhemoglobin levels of nonsmokers. Stewart et al.[1-3] noted that 45% of all the nonsmoking blood donors tested had carboxyhemoglobin saturations of more than 1.5%. This conclusion has been challenged by other investigators[4,5] who question the accuracy of the technique used by Stewart et al.[6]

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for the measurement of carboxyhemoglobin. The absolute values of carboxyhemoglobin levels are questionable. Even though the technique is accepted, the levels demonstrate the combined amount of endogenous (formed in the body) and exogenous sources of carbon monoxide (from cigarette smoking, vehicular emissions and occupational exposure).

Median and 90% range of carboxyhemoglobin saturation

Location	Cigarette Smokers	Nonsmokers	Δ Median
Anchorage	4.7 (0.9-9.5)	1.5 (0.6-3.2)	3.2
Chicago	5.8 (2.0-9.9)	1.7 (1.0-3.2)	4.1
Denver	5.5 (2.0-9.8)	2.0 (0.9-3.7)	3.5
Detroit	5.6 (1.6-10.4)	1.6 (0.7-2.7)	4.0
Honolulu	4.9 (1.6-9.0)	1.4 (0.7-2.5)	3.5
Houston	3.2 (1.0-7.8)	1.2 (0.6-3.5)	2.0
Los Angeles	6.2 (2.0-10.3)	1.8 (1.0-3.0)	4.4
Miami	5.0 (1.2-9.7)	1.2 (0.4-3.0)	3.8
Milwaukee	4.2 (1.0-8.9)	1.2 (0.5-2.5)	3.0
New Orleans	5.5 (2.0-9.6)	1.6 (1.0-3.0)	3.9
New York	4.8 (1.2-9.1)	1.2 (0.6-2.5)	3.6
Phoenix	4.1 (0.9-8.7)	1.2 (0.5-2.5)	2.9
St. Louis	5.1 (1.7-9.2)	1.4 (0.9-2.1)	3.7
Salt Lake City	5.1 (1.5-9.5)	1.2 (0.6-2.5)	3.7
San Francisco	5.4 (1.6-9-8)	1.5 (0.8-2.7)	3.9
Seattle	5.7 (1.7-9.6)	1.5 (0.8-2.7)	4.2
Vermont, New Hampshire	4.8 (1.4-9.0)	1.2 (0.8-2.1)	3.6
Washington, DC	4.9 (1.2-8.4)	1.2 (0.6-2.5)	3.7

b. Significance of carboxyhemoglobin levels of smokers. Stewart et al.[1-3] reported that the median for carboxyhemoglobin saturation for smokers ranged

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from 3.2 to 6.2%. These investigators also observed that the carboxyhemoglobin levels were influenced by the quantity of tobacco used in the previous 24 hours as well as by the time elapsed since the last cigarette smoked. One hour after the last cigarette, the mean values for carboxyehmoglobin saturation in cigarette smokers were as follows:

Location	Non-smoker	Smoker: packs of cigarettes smoked per day				
		<1/2	1/2-1	1	1 1/2	2
Milwaukee	1.3	3.0	4.2	5.3	6.2	4.7
New Hampshire and Vermont	1.4	3.3	4.4	5.7	6.7	5.3
New York City	1.4	3.1	4.3	4.7	5.8	6.3
Washington, DC	1.4	3.8	4.6	5.2	5.8	6.6
Los Angeles	2.0	4.0	5.2	6.0	7.4	7.5
Chicago	2.0	4.8	5.4	6.3	7.1	7.7

The above numbers are quoted from the original article by Stewart et al.[1] There are no reported Ranges or Standard Deviation to evaluate the results for statistical significance. The groups of smokers from Milwaukee do not show a dose-response curve; the mean carboxyhemoglobin saturation for smokers of 1 1/2 packs per day was higher than those consuming 2 packs per day. The 2-pack smokers from New Hampshire and Vermont have lower mean saturation than the 1-1/2 pack smokers. Smokers in urban areas such as New York City and Washington have mean saturation levels about the same as smokers in rural states (New Hampshire and Vermont). These values conflict with what has been reported by other investigators. The conclusions of this study apply only to the selected group of blood donors and not to the general population of smokers and nonsmokers.

c. Significance of difference between smokers and nonsmokers. Stewart

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et al.[1] recognized that carboxyhemoglobin saturation can be influenced not only by geographical location of the individual, but also by the existing meteorological conditions and the occupation of the individuals. It has not been possible to match the occupational and environmental factors for the smokers and nonsmokers for each metropolitan area so that the difference in blood levels cannot be ascribed to smoking alone. The contributions of vehicular traffic and occupational sources of carbon monoxide to blood carboxyhemoglobin levels are discussed elsewhere (Chapters 6 and 7).

2. Metropolitan St. Louis Survey by Kahn, Wallace and Collaborators.

Blood samples from blood donors in the St. Louis area were collected for a 12-month period in 1971 and 1972. Kahn, Wallace and their collaborators reported the mean carboxyhemoglobin saturation for 16,649 donors. The mean and standard errors were as follows:

	COHb % Saturation
Total sample (16,649)	2.30 ± 0.02
Nonsmokers (10,157)	0.85 ± 0.01
Smokers (6,492)	4.58 ± 0.03

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The levels reported above are different from those observed by Stewart et al.[1-3] for 500 blood donors from St. Louis (see above). The median values were 1.4 for nonsmokers, and 5.1 for smokers. It is on this basis that Kahn et al.[4] questioned the accuracy of the technique used by Stewart et al.[6] who overestimated the carboxyhemoglobin levels in the blood samples.

Kahn et al.[7-11] have identified several factors that correlated with the carboxyhemoglobin levels. They are as follows: occupational exposure, socioeconomic data, travel time or distance, racial difference and ambient carbon monoxide levels.

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Although the carboxyhemoglobin levels of smokers were higher than nonsmokers, the difference is not caused by smoking alone. Kahn et al.[8] reported data indicating that industrial occupation and the type of tobacco smoked influence the carboxyhemoglobin levels. There are also differences between sexes; when men and women smoke at the same rate and reach the same equilibrium level of carboxyhemoglobin, women achieve lower levels after ceasing smoking for the day. Physiological differences such as blood volume, hemoglobin, pulmonary vital capacity and carboxyhemoglobin excretion, in addition to varying ambient exposures associated with travel and employment were suggested as explanations for the differences in male and female post-smoking carboxyhemoglobin values.

3. Survey in Israel by Torbati et al.

A group of 500 male Israeli blood donors were examined by Torbati et al.[12] The mean and Standard Deviation of carboxyhemoglobin saturation are as follows:

nonsmokers (231 subjects)	0.70 ± 0.71
smokers (269 subjects)	3.43 ± 1,69

In addition to the above results, there was also a correlation noted between blood levels and occupational exposure to carbon monoxide for both smokers and nonsmokers. These conclusions are essentially similar to those based on American donors (see above).

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4. Interpretation of Carboxyhemoglobin Levels of Blood Donors.

The results of the surveys indicate that carboxyhemoglobin levels of

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smokers are higher than nonsmokers. However, there is no agreement as to a mean or median value for carboxyhemoglobin saturation. For metropolitan St. Louis, the mean for 16,649 donors is 4.58 (see 2 above); for 18 cities, the medians range from 3.2 to 6.2 (see 1 above); and for Israel, the mean is 3.43% saturation (see 3 above). The variability in reported mean or median values is a reflection of the degree of exposure to carbon monoxide in the ambient air which differs in various cities. A single blood analysis does not reflect the mean level during a 24-hour period. The technique used by one group of investigators has been criticized by Radford et al.[5] and by Cole[13] as being capable of errors and inaccurate so that the reported mean and median values may be overestimations of the true carboxyhemoglobin levels of smokers.

It is important to point out that the elevation of carboxyhemoglobin levels in smokers has led to the suggestion that they should not be used to donate blood.[14] On the other hand, it is recognized that the amount of carboxyhemoglobin is small and is diluted by the blood volume of the recipient and that carbon monoxide is ultimately eliminated from the recipient.[15,16] Even more importantly, there is no agreement on the consequence of low levels of carboxyhemoglobin that would be expected from the recipient. There is no evidence that the elevation of carboxyhemoglobin saturation in the donors blood is a hazard to the recipient.

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B. Carboxyhemoglobin Levels in Smokers

The results of analysis of blood samples from donors described in the preceding section represent the most recent attempts to show that smokers are likely to absorb carbon monoxide in the course of inhaling cigarette smoke. From the historical standpoint, it should be recalled that Wahl,[17] in 1899, was the first to demonstrate the presence of carbon monoxide in cigarette smoke and that Hartridge,[18] from 1919 to 1920, was the first to identify carboxyhemoglobin in the blood of smokers. The subsequent developments in this area of investigation are reviewed in this section.

1. Carbon Monoxide Content of Cigarette Smoke.

In the initial investigation by Wahl,[17] the presence of carbon monoxide in tobacco smoke was demonstrated by exposing a few drops of blood to 2 or 3 mouthfuls of tobacco smoke, and detecting carboxyhemoglobin by spectroscopy. A more direct approach has been to measure the amount of carbon monoxide from burning tobacco the results of which are as follows:

Investigators (year)	ml carbon monoxide/g tobacco
Marcelet (1907)[19]	20-80
Lee (1908)[20]	4.1
Lehmann (1909)[21]	15-23.5
Baumberger (1923)[22]	8.3
Ehrismann and Abel (1934)[23]	17.25-35
Saruta (1937)[24]	62.7
Kohn-Abrest (1949)[25]	40.0

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The total amount of carbon monoxide ranged from 4 to 80 ml per g of tobacco.

Subsequent analysis for carbon monoxide has been expressed as percentage contained in the cigarette smoke. The results are as follows:

Investigators (year)	% carbon monoxide
Armstrong (1922)[26]	0.8-1.24
Philippe and Hobbs (1956)[27]	2.8-5.7
Osborne et al. (1957)[28]	3.3-5.7
Mumpower et al. (1962)[29]	5.1
Newsome and Keith (1965)[30]	5-11
Jarrell and Burde (1965)[31]	0.5-1.0
Harke and Drews (1968)[32]	3.4-7.7
Kruszynski and Henriksen (1969)[33]	3.5-8.1
Otsuka et al. (1970)[34]	1.6-5.6
Morie (1973)[35]	4.25-5.35

The above results show a wide range of values among various investigators, because of the differences in collection of smoke and the technique for analysis of carbon monoxide. For the same investigator, there is still a variation in concentration of carbon monoxide depending on the type of tobacco, speed of burning the cigarette, and the amount of air diluting the smoke. Even for the same cigarette, there is an increase of carbon monoxide concentration as the cigarette burns closer to the butt or filter tip.[36-40]

The porosity of the cigarette paper can also influence the concentration of carbon monoxide in the cigarette smoke.[41-43] The nature of the filter also alters the amount of carbon monoxide generated.[44-46] These figures,

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if accurate, are reflective of only the precise conditions of type of tobacco, volume and frequency of the inspired smoke, porosity of the paper and the nature of the filter. A slight variation in any component would change the concentration of carbon monoxide in the cigarette smoke.

2. Amount of Carbon Monoxide Absorbed in the Lungs.

The cigarette smoke in the mainstream, although inhaled in its undiluted form, is immediately mixed by the air in the lungs of the smoker. The first estimation of the amount of carbon monoxide absorbed by cigarette smokers was made by Baumberger in 1923 by comparing the concentration of inhaled smoke and the expired air. In a group of six subjects, about 61% of the carbon monoxide was absorbed.[47] Bokhoven and Niessen reported absorption of 82 to 87% in three subjects,[48] whereas, Dalhamn et al. reported a carbon monoxide retention of 54 ± 12.7% in five subjects.[49] These results refer to the amount of carbon monoxide of the smoke that has been diluted by the alveolar air.

The above results are not surprising because carbon monoxide diffuses readily across the alveolar membrane and combines readily with hemoglobin. However, the above observations were not accompanied by measurements of carboxyhemoglobin saturation in the blood to determine whether the amount absorbed is significant enough to elevate the carboxyhemoglobin saturation. Even if there should be a significant elevation in carboxyhemoglobin, it would be disposed of in the same manner as the carbon monoxide absorbed from the ambient air derived from sources other than cigarette smoke. The rates of disposition of carbon monoxide from various sources have not been examined simultaneously with absorption studies.

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3. Carboxyhemoglobin Levels Associated with Cigarette Smoking.

In the face of varying concentrations of carbon monoxide in the cigarette smoke, the disparate frequency of smoking and the volume of smoke inhaled that is diluted with alveolar air, and a wide range of absorption of carbon monoxide (54 to 87%), it is not surprising to note that the reported levels of carboxyhemoglobin of smokers are as varied. The results, as they relate to the environmental level of carbon monoxide which vary according to the geographical location of the study, are as follows:

City and Investigators	No. of subjects = mean (range) COHb nonsmokers	smokers
Chicago Hanson and Hastings (1933)[50]	7=1.5 (1.2-1.9)	9=2.1 (2.0-6.7)
Boston Gaensler et al. (1957)[51]	9= (0.6-1.2)	10= (3.1-7.8)
Los Angeles Motley (1971)[52]	115=1.5 (0.2-2.9)	81=5.7 (3.2-14.2)
Sunderland, Great Britain Trinder and Harper (1962)[53]	23=0.9 (0.4-2.1)	15=2.6 (0.7-6.5)
Munich, Germany Scheidemandel and Daum (1973)[54]	26=2.4 (1.6-5.0)	19=7.4 (2.8-13.4)
Milan, Italy Parmeggiani and Gilardi (1952)[55]	9=2.8 (0-4.0)	14=4.9 (1-9)
Genova, Italy Kanitz et al. (1973)[56]	164=1.2 (0.2-3.3)	34=2.3 (0.5-6.1)
Tokyo, Japan Muroya and Kubota (1974)[57]	30=0.7 (0-3.3)	28=3.5 (0.9-8.3)
Zagreb, Yugoslavia Valic and Duric (1954)[58]	75=0.9 (0-2.4)	75=3.8 (0-5.7)

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The above results show the wide range of values for smokers. In each series of comparisons, the range for smokers is two to seven times the range of nonsmokers value for carboxyehmogolbin levels. The wide range is, in part, caused by the fluctuation of carbon monoxide in the mainstream that is diluted by the inspired

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air in the course of smoking a cigarette. Furthermore, the pattern of frequency and volume of smoking a cigarette, and the total daily consumption varies from smoker to smoker so that it is not surprising that carboxyhemoglobin levels differ widely among smokers.

a. Time-blood carboxyhemoglobin relationships. There are a few studies which include more than one sampling of blood for carboxyhemoglobin analysis.[59-61] The results indicate a rise followed by a fall in carboxyhemoglobin saturation in the course of smoking a cigarette. Ashton and Telford[62] analyzed four to six finger-prick samples in the course of 20 min for each of five smokers. The peak level was reached immediately after consuming one cigarette which was followed by a fall with half recovery to control level in about 5 to 15 min.

Castleden and Cole[63] inserted an indwelling venous cannula in each of six smokers. By repeated analysis of the blood, the carboxyhemoglobin level remained fairly constant throughout 24 hours, and there was no rise at the end of the day. That each smoker maintains his carboxyhemoglobin level challenges the theory of Goldsmith et al.[64-66] and others[8,67,68] that with repeated smoking in the course of a day, there would be a gradual buildup of carboxyhemoglobin. This theory is based on analysis of alveolar air[64-71] carbon monoxide as well as several assumptions which have not been supported by actual blood analysis by Castleden and Cole.[62]

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The above observations support the theory that smokers fix a level of carboxyhemoglobin saturation that is not exceeded in the course of a day. Reducing the carbon monoxide content of cigarette smoke might mean that a given individual could then smoke more without violating his personally-set level.

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b. Dose-response relationships. There is no consistent relationship between the amount of cigarettes consumed and carboxyhemoglobin levels. An examination of the range of values indicates that there is a considerable amount of overlapping. For instance, Balbo et al.[72] reported the following results derived from Parisian volunteers.

Amount cig. (no. subjects)	Mean	Range
nonsmokers (44)	1.9	0-7
5 cigarettes daily (34)	2.1	0-9
10 cigarettes daily (32)	2.2	0-9.5
15 cigarettes daily (16)	2.2	0-5.9
20 cigarettes daily (20)	2.2	0-6.9
30 cigarettes daily (7)	2.8	0-5.2

The other reports do not show range of values for various groups of smokers.[73-75] The presence of a dose-response relationship is questionable unless the results are subjected to statistical analysis.

C. Practical Aspects of Carboxyhemoglobin Level

That carbon monoxide present in cigarette smoke is absorbed in the blood of smokers has prompted several investigators to suggest means of reducing the carbon monoxide emitted from cigarettes.[76-78] However, it should be noted that the amount absorbed by the smoker is to a large extent influenced by the manner of smoking. Robinson and Forbes[79] concluded that puff volume influences the delivery of carbon monoxide from cigarettes, just as does the porosity of the cigarette paper.

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Another suggestion has been to publicize the relative amount of carbon monoxide emitted from cigarettes, in the same manner as nicotine and tar contents are stated. The pros and cons have been discussed in correspondence published in Journals.[80-89] In addition to the factors that influence carboxyhemoglobin blood levels discussed in this chapter, there is an additional factor: the alteration of nicotine in the cigarette influences the consumption of cigarettes and, in turn, the carboxyhemoglobin level.[90-94] A change in the carbon monoxide content of cigarette smoke influences the smoking pattern and cigarette consumption of the individual, as though there is a self-regulating factor that keeps carboxyhemoglobin at a level that is constant for a particular smoker. More investigation is needed to determine the factors responsible for a relative fixation of carboxyhemoglobin levels in smokers. The fundamental issue thus far resolved is the health consequence of increasing or reducing the carbon monoxide in cigarette smoke. This question is answered in the next two chapters.

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Chapter 3

CARDIOVASCULAR SYSTEM

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In recent years, there has been a considerable amount of attention directed at the cardiovascular effects of carbon monoxide in general and in particular to that inhaled while cigarette smoking. The two-hundred articles cited in this chapter are those that relate to this subject. However, only about 10% of these articles relate directly to carbon monoxide in cigarette smoke. The remainder of the articles are on the effects of carbon monoxide without the components of cigarette smoke.

The cardiovascular effects of carbon monoxide have, therefore, been examined as a single chemical, usually administered in concentrations much higher than those experienced in the course of cigarette smoking. The inhalation of lethal quantities of carbon monoxide causes cardiac arrest. The highest concentration that does not exert toxicity on the heart has been difficult to ascertain since various experiments in several animal species have resulted in varying threshold limits. The least conservative estimate states that the carbon monoxide contained in cigarette smoke is harmful to the heart of the smoker. This is the opinion of four groups of scientists and is discussed in the sections below. (a) Aronow, who claims that carbon monoxide aggravates coronary heart disease; (b) Wald, who describes a correlation between carboxyhemoglobin level and the incidence of arterial disease; (c) Ayres, who noted a depression of cardiac function in the experimental heart preparation perfused with blood containing high levels of carboxyhemoglobin; and (d) Astrup and Kjeldsen, who have identified arteriosclerotic lesions in rabbits fed with cholesterol and exposed to carbon monoxide.

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The four conclusions taken as a group have convinced some authorities to subscribe to the proposition that carbon monoxide contained in cigarette smoke causes cardiac disease, specifically angina pectoris and myocardial infarction. These authorities have overlooked the fundamental feature of most of their experimental observations as stated above, i.e. they used carbon monoxide inhalation, a procedure that does not relate directly to cigarette smoke. Furthermore, there has been no confirmation of the four concepts and there are even conflicting results which question the validity of the experimental evidence supplied by the four investigators mentioned above.

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A. Angina Pectoris

The most frequently-cited evidence that carbon monoxide contained in cigarette smoke is harmful to the heart is the series of experiments conducted by Aronow et al. Since 1969, they have been studying patients with angina pectoris on maximal treadmill exercise.[1-14] The patients inhaled smoke from cigarettes of varying nicotine content, as well as carbon monoxide administered as a mixture from a compressed air tank or by exposing the patient in a freeway.

In recent review articles,[15-22] Aronow has concluded that "nicotine and carbon monoxide both aggravate angina pectoris and contribute to increased incidence of fatal and nonfatal myocardial infarction and sudden death from coronary heart disease in cigarette smokers."[19] Aronow based his conclusion relating to myocardial infarction and sudden deaths on observations by selected investigators, ignoring the conflicting results of others (see B). Aronow's own studies on aggravation of angina pectoris have not been confirmed. This section reviews the contradictions to Aronow's conclusion that "nicotine and carbon monoxide both aggravate angina pectoris."

1. Exercise Performance.

The basic test used by Aronow et al. measures the duration of time that a subject can tolerate exercise on a treadmill. The endpoint of the procedure

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is a subjective one, i.e. chest pains, and has been criticized by Theodore,[23] Garfein and Dwyer[24] and Lescoe.[25] The last-mentioned cardiologist cited Aronow's own remarks to a newspaper reporter that the subjective exercise performance test can be improved in half of his patients receiving a placebo. There are serious inconsistencies in the results of Aronow's experiments which are as follows:

a. Intensity of reduction of exercise performance. An examination of the results of Aronow et al. indicates the following changes in exercise performance as a result of exposing anginal patients to carbon monoxide or cigarette smoke:

	Exercise time in sec. ± SD		
(No. of patients) procedure	control	exposure	Δ
(10) breathing freeway air[7]	249 ± 82	174 ± 87	75
(10) 50 ppm carbon monoxide[8]	224 ± 43	187 ± 36	37
(10) marihuana cigarette[12]	244 ± 16	129 ± 13	115
(10) high-nicotine cigarettes[14]	241 ± 51	185 ± 43	56

When the results of four publications appearing from 1972 to 1975 are examined as a group, the most surprising feature is the consistency of mean control exercise time from 224 to 249 sec. The publications do not state whether the same ten patients were used from study to study. In any event, the smoking of a high-nicotine cigarette caused a shortening of mean exercise time by 56 sec, which is slightly higher than the standard deviation (51) of the control values.

There is no confirmation that cigarette smoking reduced the exercise per-

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formance of anginal patients. With low levels of carbon monoxide, Anderson et al.[26] observed no effect of 50 ppm inhalation but shortening of exercise performance after inhalations of 100 ppm. It is significant that Anderson et al did not find a difference in response to carbon monoxide exposure between anginal patients who were smokers and those who were nonsmokers.

Aronow et al.[7, 8, 12, 14] and Anderson et al.[26] are the only investigators who have used the shortening of exercise time to provoke angina pectoris as a sign that low levels of carbon monoxide are harmful to the anginal patient (see next paragraph). It might be argued that the earlier onset of pain may also be desirable because there is an earlier warning to the patient to stop exertion. The stimulus that excites anginal pain has not been identified although there is recent evidence to implicate coronary vasospasm (Kattus[27]). Carbon monoxide and nicotine can be excluded as causative agents because these constituents of cigarette smoke do not constrict the coronaries.

b. Carboxyhemoglobin levels of anginal patients. Another surprising feature of the results of Aronow et al. is the uniform mean arterial blood carboxyhemoglobin levels and low standard deviation from study to study:

number of subjects	COHb % saturation mean ± S. D. arterial blood	venous blood
(10) angina; 3 smokers, 7 nonsmokers[7]		0.83 ± 0.23
(10) angina; all nonsmokers[8]	1.03 ± 0.27	
(10) intermittent claudication; 2 smokers, 8 nonsmokers[9]	1.08 ± 0.24	

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number of subjects	COHb % saturation mean ± S. D. arterial blood	venous blood
(8) angina; all smokers[11]	2.28 ± 0.46	2.16 ± 0.45
(10) angina; all smokers[12]	2.43 ± 0.14	
(10) healthy; all nonsmokers[13]	1.67 ± 0.33	
(10) angina; all smokers[14]	2.19 ± 0.50	

The above results are lower than any previously-reported series of smokers and nonsmokers, both for mean values and for standard deviation (see Chapter 2). In the series of 10 anginal patients reported by Anderson et al.,[26] (the carboxyhemoglobin values for 5 smokers and 5 nonsmokers) the standard deviation was 0.6 whereas, a similar mixed group reported by Aronow et al.[7] had a standard deviation of 0.23.

There is reason to suspect that the analysis of low levels of carboxyhemoglobin performed by Aronow et al. are inaccurate especially when the results of coronary sinus blood analysis are considered together with arterial blood in 8 subjects before and after smoking each of three cigarettes or inhaling 150 ppm carbon monoxide:[11]

Procedure on 8 angina patients	arterial mean ± S. D.	venous mean ± S. D.	Δ mean
control	2.16 ± 0.45	2.24 ± 0.39	-0.08
after 1 cigarette	3.15 ± 0.51	2.81 ± 0.50	+0.34
after 2 cigarettes	3.76 ± 0.49	3.48 ± 0.53	-0.28
30 min after 2 cigarettes	3.25 ± 0.50	3.21 ± 0.50	+0.04
after 3 cigarettes	4.16 ± 0.48	3.90 ± 0.51	+0.26

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Procedure on 8 angina patients	arterial mean ± S. D.	venous mean ± S. D.	Δ mean
control	2.05 ± 0.32	2.04 ± 0.35	+0.01
after 150 ppm CO	4.21 ± 0.36	3.86 ± 0.39	+0.35

The above differences between arterial and coronary sinus blood were over looked by Aronow et al. It seems that in the same group of patients, there is either a release (as much as 0.28 vol %) or uptake (as much as 0.35%). Since the heart is not known to produce or metabolize carbon monoxide, the differences reflect an error in the analysis of as much as 0.23 + 0.35%, i.e. 0.63% carboxyhemoglobin. The error of analysis is as large as the standard deviation of the series. The carboxyhemoglobin levels reported by Aronow et al. have never been duplicated by any other cardiologist in respect to the homogenous nature of anginal patients.

c. Heart rate effects of inhalation of carbon monoxide. An analysis of the the effects of inhalation of carbon monoxide reveal the following:

subjects	mean + S. D. beats/min control	after
(10) angina breathing freeway air[7]	80.6 ± 5.0	81.8 ± 6.6
(10) angina breathing 50 ppm CO[8]	74.8 ± 75.0	75.0 ± 5.74
(8) angina breathing 150 ppm CO[11]	72.4 ± 4.7	72 ± 5.5
(10) healthy breathing 100 ppm CO[13]	74.4 ± 7.2	73.4 ± 9.6

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The above results indicate a steady state of inhalation of up to 150 ppm carbon monoxide does not influence the heart rate. Shephard[28] also reported no change in heart rate in subjects inhaling carbon monoxide to increase the carboxyhemoglobin level by 2.4 to 5.4%.

d. Heart rate effects of cigarette smoking. That nicotine caused an acceleration in heart rate was the conclusion of Aronow et al. on the basis of comparing the heart rate response to inhalation of cigarettes with varying amounts of nicotine.[6, 10, 14] The slight increase in heart rate is accompanied by a small rise in blood pressure but no increase in cardiac index. These observations confirm the earlier results of Regan et al.[29-31] Pentecost and Shillingford[32] and Summers et al.[33] In patients with coronary heart disease, although smoking caused tachycardia, there is no accompanying increase in cardiac output.

e. Coronary blood flow and myocardial metabolism. That cigarette smoking does not reduce coronary blood flow was proven by Bargeron et al.[34] who applied the nitrous oxide technique and catheterization of the coronary sinus. Cigarette smoking in 30 normal subjects caused a significant rise in coronary blood flow, a decline in coronary vascular resistance and myocardial extraction of glucose and oxygen. In 7 males with myocardial infarction, smoking still caused an increase in blood pressure and heart rate. In 3 of the patients, coronary blood flow did not change, while in 3 others, it fell slightly.[29-31] Although there was a slight increase in oxygen consumption in 3 cases, the

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myocardial efficiency was also increased. The data reported illustrate that, in patients with coronary heart disease, smoking results in no reduction of myocardial efficiency. In 15 patients with angiographically-demonstrated severe obstructive coronary artery disease, cigarette smoking did not induce lactate production by the heart.[33] There was no evidence of myocardial ischemia as determined by abnormalities in lactate extraction based on analysis of coronary arterial and sinus blood samples.

2. Electrocardiogram as a Sign of Myocardial Oxygenation.

The electrocardiogram has been used to assess the adequacy of oxygenation of the myocardium. The signs of ischemia include depression of the S-T segment, inversion of the T wave and alteration in the configuration and duration of the QRS complex. In the following paragraphs the influence of smoking on the electrocardiogram is differentiated between anginal patients and healthy individuals not suffering from coronary heart disease.

a. Precipitation of angina pectoris by cigarette smoking. Oram and Sowton[35] sent a questionnaire to 721 patients suffering from angina pectoris. The patients were asked if, in their opinion, smoking had any effect on their chest pains. Of the 309 smokers who responded, 20 experienced angina pectoris shortly after lighting a cigarette.

The 20 patients who considered that their chest pain was precipitated or aggravated by smoking were reexamined clinically and in each case, electrocardiograms were taken, as follows: A resting 12-lead record was first made.

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The electrocardiogram was repeated either after the patient had smoked until pain was induced, or after three cigarettes had been smoked consecutively. A maximum tolerance exercise test was then performed, and at its conclusion, a third record was taken. The patient was, at once, asked to smoke again, and a further record made. After a rest of about 45 minutes, a second maximum-tolerance electrocardiogram was taken. Electrocardiograms were performed in this manner so as not to miss any of those rare patients in whom smoking causes a recurrence of chest pain, recently induced by exercise, and also patients in whom, immediately after smoking, pain and electrocardiographic changes on exertion are more severe.

By this manner of investigation, only 3 patients showed electrocardiographic changes appearing after smoking and exercise. The incidence of chest pain precipitated by smoking was 6% (20 out of 309 cases); only 1% showed electrocardiographic signs of myocardial ischemia during smoking.

b. Electrocardiogram of non-anginal subjects. In healthy subjects the examination of the electrocardiogram of smokers failed to show a significant difference in frequency of the ischemic pattern in the electrocardiogram as compared with that of nonsmokers.[36-40] In similar surveys by other investigators, there were more smokers in the group that showed ischemic response in the electrocardiogram during exercise. Doyle and Kingh[41] reported that 69% of subjects giving an ischemic response were smokers, whereas, 37% of those with a normal electrocardiogram were smokers. Kattus et al.[42] obtained the

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respective incidence of 59% and 42%. As in other studies, the role of various risk factors could not be excluded. When the heart was stressed by hypoxia, there was no difference between smokers and nonsmokers in the T-area vectors of the electrocardiogram.[43] The QRS complex showed a right axis deviation in some smokers.[44] The polarcardiogram, which graphs the polar coordinates of the heart vectors vs. time, indicates a difference between smokers and nonsmokers.[45] The complexity of the technique prevents its widespread application to determine the significance of the difference.

3. Coronary Arteriography.

The effect on the coronary arteries of the smoking of cigarettes has been investigated in man by arteriography. Likoff et al.[46] tested the smoking of 2 cigarettes in each of 10 patients with coronary heart disease. No effect on the size of the vessels was observed by cineradiography.

The results of coronary arteriography in patients with angina pectoris did not show a relationship consistent with the amount of cigarette smoking. Newton et al.[47] examined 80 patients with angina pectoris and made the following observations:

43 normal arteriograms: 29 subjects were smokers.

46 abnormal arteriograms: 40 subjects were smokers.

They concluded that smoking was not related to the anatomical findings at

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coronary arteriography.

Banks et al.[48] examined 107 patients with ischemic heart disease (66%) and nonischemic heart disease (28%), most of the latter with rheumatic heart disease:

68 cases of ischemic heart disease: 39 subjects were smokers.

39 cases of nonischemic heart disease: 14 subjects were smokers.

The arteriogram was scored according to the degree of obstruction of all three coronary arteries. There was no correlation between the number of cigarettes smoked and the extent of disease in any of the arteries. Even the total coronary arterial score did not bear any significant relation to the tobacco consumption. There is, therefore, no indication by arteriography that cigarette smoking produces obstructive lesions in patients with heart disease, nor does smoking exert any coronary vasospasm.

4. Does Carbon Monoxide Provoke Angina Pectoris?

A review of the literature indicates that there is no definitive evidence to support the contention that the carbon monoxide present in cigarette smoke provokes angina pectoris in patients suffering from this disease. The widely-quoted studies of Aronow and his collaborators show a reduction in exercise performance when anginal patients either smoke cigarettes or inhale atmosphere containing carbon monoxide. The uniformity of the results derived from groups of 8 or 10 patients questions the validity of the techniques used and suggests the uniqueness of the patients used for the study. In a survey of 309 patients with

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objective recording of the electrocardiogram, only three patients showed a reduction in exercise tolerance judged by ischemic pattern of the electrocardiogram in the course of smoking cigarettes.

Tolerance to exercise was originally used for diagnosis of coronary heart disease, and not for evaluating a deterioration of the patient, such as by inhaling carbon monoxide. There have been no prospective studies showing that anginal patients who experience a reduction in exercise performance die sooner from myocardial infarction than those patients whose exercise performance improves. There is evidence to the contrary relating to patients who develop myocardial infarction (see section B).

In healthy adults, tolerance to vigorous exercise to the point of exhaustion is sometimes reduced in smokers compared to nonsmokers.[49-53] These reports are based on a limited number (10 to 20) of subjects. In larger prospective studies, cigarette smoking did not reduce the capacity to exercise. Morris et al. reported that smokers could tolerate vigorous exercise as well as nonsmokers among 16,882 office workers.[54] Gyntelberg showed that smokers had significantly higher physical fitness than nonsmokers in a group of 5,249 middle-aged Danish male workers.[55] In a group of 78 American male faculty members, Coleman et al. reported no difference in the aerobic capacity scores or physical work capacity between smokers and nonsmokers.[56] These observations indicate that measurements of tolerance to vigorous exercise on a treadmill or a bicycle ergometer to the point

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of exhaustion are not relevant to ordinary exercise and to occupational performance (see Chapter 7). A similar question can be raised in the evaluation of anginal patients by means of a treadmill which is a more vigorous form of exercise than any activity patients are ordinarily exposed to in their daily living.

B. Myocardial Infarction

The literature on myocardial infarction is almost entirely epidemiologic in nature. It has been suggested that the carbon monoxide contained in cigarette smoke is a major factor in the occurrence of myocardial infarction among cigarette smokers. An examination of relevant publications does not support this contention.

1. Association Between Atherosclerotic Disease and Carbon Monoxide Exposure.

The cross-sectional study of Wald et al.[57] on 1,085 volunteers who worked for several firms in Copenhagen is usually cited to support the hypothesis that elevation of carboxyhemoglobin levels in tobacco smokers is associated with a high incidence of atherosclerotic disease. It should be stated at the outset that the epidemiologic study consisted entirely of Danish smokers and there were no nonsmokers for comparison. There was actually no relationship between the smoking history and the incidence of ischemic heart disease. However, the carboxyhemoglobin levels in smokers were found to provide a better

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indication of the person's risk of developing atherosclerotic diseases.

The above results can be interpreted to signify that sources of carbon monoxide, other than cigarette smoke relate to the incidence of disease, rather than smoking per se. This possibility was not considered by Wald et al.[57] Instead, Wald et al.[58] described a method of evaluating exposure of smokers by combining carboxyhemoglobin measurement, the smoking history and the carbon monoxide yield produced by each cigarette. The indices of tobacco smoke absorption are based on the premise that there is a build up of carboxyhemoglobin during the day in cigarette smokers.[59] However, this method proposed by Wald et al.[57] is in question because Castleden and Cole[60] failed to show an increase in carboxyhemoglobin level during the day. In a recent review of the literature, Wald and Howard[61] reiterated their earlier conclusion that carboxyhemoglobin level is correlated with the prevalence of arterial disease, independently of the amount smoked.

In all the publications by Wald, there is no mention of a 1973 article by Rea et al.[62] who performed a community study of cardiorespiratory disease in Great Britain in a group of 783 adults which included smokers and non-smokers. Although the level of carbon monoxide in the expired air correlated with the amount of cigarettes smoked, there was no correlation between carbon monoxide level and the symptoms of ischemic heart disease. This study is an important one because it is the only one published that examines carbon

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monoxide exposure and incidence of heart disease in smokers and nonsmokers.

2. Association Between Carboxyhemoglobin Levels and Myocardial Infarction.

In the Los Angeles area, Cohen et al.[63] studied the case fatality rates for patients admitted to hospitals with myocardial infarction. The results indicate that there is an increased fatality rise in high pollution areas during periods of relatively increased carbon monoxide pollution. These observations prompted Haywood et al.[64] to design a study at the Los Angeles County Medical Center. In 34 infarction patients and 35 control patients, there was no difference in carboxyhemoglobin level although there was a higher percentage of smokers in the infarction group.

Kuller et al.[65,66] concluded a study of the relationship between carbon monoxide exposure and heart attacks in the city of Baltimore. Unlike the results in Los Angeles, there was no correlation between the number of cases per day and the ambient carbon monoxide levels. Postmortem carboxyhemoglobin levels were slightly higher in arteriosclerotic heart disease deaths than in sudden deaths due to other causes, the higher levels appearing in smokers.

The above observations indicate that the incidence of myocardial infarction is not correlated with carbon monoxide exposure. That there are more smokers among fatalities does not mean that smoking is the cause. An examination of results of retrospective and prospective studies does not support a cause and effect relationship between smoking and myocardial infarction.

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a. Retrospective studies of myocardial infarction deaths. Spain et al.[67] examined a group of 102 men who died suddenly of acute myocardial infarction. The average age at the time of death was 16 years less in those who smoked heavily than it was in the nonsmokers. Porsteinsson et al.[68] reviewed a group of 119 men and 32 women who died of myocardial infarction. The average age at the time of infarction was 57.9 for smokers, 62.1 for exsmokers and 69.2 for nonsmokers. Spain et al.[67] have discussed two explanations for the occurrence of sudden death among smokers at a younger age than among nonsmokers. They discounted alteration in coagulability of the blood by smoking on the basis that the incidence of recent coronary arterial thrombi was not correlated with smoking habits. They favor the explanation that smokers as a group are, in many respects, different types of individuals from nonsmokers. This is supported in their study by the fact that the average age at which those who smoked heavily were involved in and died on account of accidents, suicide and homicide was 9 years less than the average age at which nonsmokers died because of similar events.

Survival time. Spain[69] and Spain and Bradess[70] examined 88 autopsy cases of sudden death following acute infarction. Their results were as follows:

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number of autopsy cases		(Survival rate)
18 nonsmokers:	12 survived < 1 hour and 6 survived > 8 hours	(33.3%)
30 smokers (<1 pack):	22 survived < 1 hour and 8 survived > 8 hours	(26.6%)
40 smokers (>1 pack):	38 survived < 1 hour and 2 survived > 8 hours	(5.0%)

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Survival time was decreased in the heavier smokers. The association was less evident within the older age brackets and more striking under the age of 50.

Paras Chavero et al.[71,72] reported 106 men who had myocardial infarction. The mortality during the acute episode was as follows:

14 nonsmokers:	2 deaths (14.0%)
10 smokers (<1 pack):	1 death (5.5%)
68 smokers (> 1 pack):	11 deaths (16.2%)

Smokers consuming less than one pack daily have a lower incidence of sudden death than nonsmokers.

b. Prospective studies of patients with myocardial infarction. Although there are more cigarette smokers in patients who suffer myocardial infarction than in control groups, there is no evidence that the smokers have a more severe form of the disease. An examination of prospective studies of patients who have suffered from myocardial infarction question a cause and effect relationship between smoking and coronary arterial disease.

Patients who survive the first 24 hours after acute myocardial infarction have been examined to determine whether cigarette smoking influenced their prognosis. The conclusion has been uniformly negative. Cole et al.[73] examined 285 patients. Statistics of smoking habits were obtained for nonsmokers and smokers respectively, as follows:

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17 nonsmokers	29.4% died within 2 months	29.4% lived over 10 yrs
31 smokers (<1 pack)	9.6% died within 2 months	41.9% lived over 10 yrs
21 smokers (>1 pack)	14.3% died within 2 months	57.0% lived over 10 yrs

The above results show that nonsmokers did not have a better prognosis than smokers. In fact, the contrary is suggested, namely, among those who develop myocardial infarction, smokers are more apt to live longer than nonsmokers.

The duration of survival of patients following an acute myocardial infarction has been examined by other groups. The Coronary Drug Project Research Group[74] studied a total of 2,181 men. There was no association between smoking and prognosis. De Soldati et al.[75] examined 66 cases of acute myocardial infarction and noted the following mean duration of survival:

17 nonsmokers		44.5 months
49	smokers (<1 pack)	99.6 months
	smokers (>1 pack)	56.7 months

The differences between groups were statistically significant. It can be noted that the duration of survival of [illegible] smokers is longer than that of nonsmokers.

The electrocardiograms of 175 men who survived a year without recurrence after a first myocardial infarct were examined for periods ranging from 1 to 4 years.[76] In the absence of recurrence, 10.9% at the end of 1 year and 20.0% at the end of 4 years had a normal electrocardiogram. There was no relation

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between the return to normal and the extent of smoking after infarction.

The electrocardiogram reflects the severity of infarction and this, in turn, influences the prognosis. Royston[77] examined at autopsy the severity of infarction of 200 hearts. The extent of damage was graded in increasing order of I, II and III. The results of that author based on smoking habits that were known for 156 cases were as follows:

32 nonsmokers:	I 54%	II 42%	III 4%
23 smokers (light)	I 52%	II 43%	III 5%
68 smokers (moderate):	I 62%	II 35%	III 3%
33 smokers (heavy):	I 61%	II 39%	III 0%

The severity of the infarct did not appear to be affected by the smoking habits.

In a study of 400 patients with myocardial infarction, Helmers[78] found no significant difference between the percentage of smokers and nonsmokers among survivors studied the first 23 hours, from 2 days until discharge, and from discharge to 3 years. Reynertson and Tzagournis[79] in a five-year prospective study of 135 patients, were also unable to find any relationship between coronary heart disease mortality rates and smoking habits prior to or after infarction.

3. What is the Significance of Carboxyhemoglobin Levels in Patients with Myocardial Infarction?

A review of the literature on myocardial infarction indicates that the carboxyhemoglobin levels in patients with myocardial infarction is an incidental finding. Some epidemiologic studies indicate a correlation between incidence of myo-

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cardial infarction and carboxyhemoglobin levels whereas others do not support a concurrence. That majority of patients happens to be cigarette smokers may be explained by the genetic or constitutional hypothesis originally suggested by Fisher in 1959, i.e. individuals are born with a genetic make up that is responsible for the acquisition of the smoking habit and also predisposes them to developing coronary heart disease.[80] The twin registry has been established in Sweden and has afforded an opportunity to examine the role of a genetic factor in predisposing a person to smoking and to diseases. A comparison between the smoking habits of 59 pairs of adult monozygotic twins and 59 pairs of adult dizygotic twins showed a significantly-greater concordance within the monozygotic pairs.[81] These results indicate the importance of the genotype in regard to acquisition of the smoking habit.

The relation of heredity to coronary heart disease in 193 twins was examined by Lundman.[82] The series was small, so that it was impossible to draw definitive conclusions regarding heredity and the disease. In a larger series of 9,168 twin pairs, the studies of a population of first-born twins revealed an increased incidence of angina among male smokers in urbanized areas that was 1.50 times that of smokers in rural districts. No difference between areas was found with respect to nonsmokers; therefore, the combination of smoking and the urban factor seems to be associated with the symptom of angina. Since there was no difference in incidence of angina in smoking discordant-twin pairs, it is unlikely that there is a causal relationship.[83-85] There was a

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higher concordance rate among monozygotic twin pairs with regard to angina pectoris than among dizygotic twin pairs, which suggests the existence of a genetic predisposition for the development of coronary heart disease.[86]

Additional data from the Swedish twin study has been reported by Friberg et al.[87] They found an excess coronary heart disease mortality among smokers in dizygotic twins with different degrees of smoking, but no excess in monozygotic twins. The authors suggest that these results support the theory originally proposed by Fisher[80] that predisposition to smoking and to coronary heart disease may be caused by a common genotype.

C. Cardiac Effects of Carbon Monoxide, Nicotine and Cigarette Smoke

Thus far, this chapter has been devoted entirely to the investigation of the effects of carbon monoxide and cigarette smoke in patients with angina pectoris or myocardial infarction. The supposition that carbon monoxide contained in cigarettc smoke provokes an anginal attack and causes acute myocardial infarction is based not only on the material already covered (A and B) but on additional misconceptions derived from interpretation of results from human and animal experimentation. The effects of carbon monoxide are equated with those of cigarette smoke, although the latter also contains nicotine. This section reviews the pharmacologic actions of carbon monoxide separately

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from nicotine to arrive at the combined action of cigarette smoke.

1. Carbon Monoxide.

In human cases of carbon monoxide poisoning, there are abnormalities in the electrocardiogram indicating myocardial ischemia. These appear when carboxyhemoglobin levels exceed 50% which is high enough to produce loss of consciousness.

In dogs, the threshold saturations that produce cardiac changes were determined by Ehrich et al.[88] There was depression of the R-T segment and degenerative changes appeared at 40% carboxyhemoglobin lasting for a few hours. Heart block and myocardial hemorrhages and necroses were observed only when the carboxyhemoglobin level exceeded 75% for one hour or longer. In rats poisoned with 10,000 ppm carbon monoxide inhalation for 10 min, high enough to elevate carboxyhemoglobin to 65%, ultrastructural changes in the heart, consisting of intracellular edema, swelling of mitochondria and disruption of lysosomes, were reported. Suzuki[89] concluded that the effects of carbon monoxide on the heart result not only from hypoxemia but also from the direct toxic effects on the specific respiratory enzymes. In 24 hours after the inhalation, the hearts of most rats appeared essentially normal so that the toxic effect was reversible.

There has been no report of cardiac arrhythmia in cases of carbon monoxide poisoning with carboxyhemoglobin less than 20,000 ppm. In anesthetized dogs, Kaul et al.[90] failed to note any electrocardiographic changes at 20 to 35%,

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carboxyhemoglobin and there was no increase in vulnerability of the ventricles to hydrocarbon-epinephrine arrhythmia or to digitalis-induced fibrillation.

Levels below 20% carboxyhemoglobin in the anesthetized dog caused an increase in cardiac output and in coronary blood flow.[91-93] The threshold for the increase in cardiac output is about 10% carboxyhemoglobin and disappears at 20%.[94] The increase in coronary blood flow occurs linearly between 4 and 20% carboxyhemoglobin.[95] Myocardial contractility is increased at 5% carboxyhemoglobin to about the same extent as that during inhalation of low oxygen. The increase in contractility appears even up to 15% carboxyhemoglobin saturation.[96]

The above results are derived from animal experiments, some with open chest and the heart depressed by the use of general anesthesia. Yet, there is no sign of cardiac depression. There are no corresponding observations on the acute effects of carbon monoxide on the ischemic heart to determine whether there is any change in response.

2. Nicotine.

The effects of nicotine can be readily demonstrated in animals and human subjects. Since nicotine is primarily a cardiac stimulant, it has been suggested that the alkaloid would provoke angina and trigger acute myocardial infarction.

a. Myocardial contractility and cardiac output. The intravenous injection of nicotine causes an increase in myocardial contractility and cardiac output.

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The mode of action has been established as due to stimulation of nicotinic receptors in the sympathetic ganglia, in the heart muscle and in the adrenal medulla.[97] The release of catecholamines from the heart is suspected of being harmful because of the increase in oxygen consumption of the heart and the ultimate depletion of the amines leading to failure of cardiac function.

There are several weaknesses in the hypothesis that nicotine by its action on the heart muscle would cause acute myocardial infarction in the tobacco smoker. The amount of nicotine absorbed during smoking is considerably less than the dose injected to elicit cardiac stimulation. It is difficult to sustain an increase in nicotine level in the blood because this alkaloid is readily metabolized after absorportion from cigarette smoke.

Frankl et al.[98] showed that smoking of cigarettes does not increase the cardiac output of patients who are predisposed to infarction. Furthermore, the release of catecholamines by nicotine does not lead to depletion. In the guinea pig heart subjected to chronic nicotine administration, there was an increase in synthesis of norepinephrine, the transmitter substance.[99] In the rabbit heart, nicotine causes the release of prostaglandin E which, in turn, would inhibit the release of norepinephrine.[100] These recent results suggest a new mechanism by which nicotine can elicit "autoinhibition" of the primary release of norepinephrine.

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b. Coronary circulation. Although the early observations that nicotine causes coronary vasospasm in the perfused isolated heart have been disproven by subsequent experimentation, some authorities continue to characterize

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nicotine as producing coronary insufficiency. Bing and his collaborators have used several techniques to show that there is no reduction in coronary blood flow and that there was a significant correlation between supply and demand of oxygen of the canine and feline hearts following the administration of nicotine.[101-104] There is, therefore, no experimental proof to suggest that nicotine causes coronary insufficiency.

3. Cigarette Smoke.

When carbon monoxide and nicotine are absorbed in the lungs in the course of smoking cigarettes, there is reason to expect an interaction between the pharmacologic actions of the alkaloid and the gas, There are no specific observations of interaction in man, except to recall that cigarette smoking in a patient with heart disease causes either an increase of cardiac output if low, or a decrease if output is high, prior to smoking. When Gould et al.[105] described these effects, they could not offer an explanation because nicotine was known to be a depressant. It appears that a patient with heart disease and abnormal cardiac output responds in the direction to normalize cardiac output.

One suggestion for the correction of an abnormal cardiac output brought about by smoking is to consider the possibility that the multiple actions of nicotine on the heart are antagonistic. If the heart has an abnormal rhythm due to abnormalities in conduction, nicotine would facilitate conduction as reported by Bekheit and Fletcher,[106] whereas, carbon monoxide would slow

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conduction, a manifestation of excessive carboxyhemoglobin.[107-109] In the isolated perfused heart, Procita and Ingenito[110] could also demonstrate a depressant effect of carbon monoxide overcome by the stimulant action of nicotine. The observations of Ilebekk and Mjos[111-113] that experimental ischemia of the dog heart is exaggerated by nicotine by increasing the myocardial uptake of free fatty acid should be extended to test whether carbon monoxide would prevent this metabolic action of nicotine. This possibility is not a remote one because there are observations that metabolism of free fatty acid by blood vessels is influenced by carbon monoxide, as described in the next section.

D. Experimental Atherosclerosis

The statement that carbon monoxide contained in cigarette smoke causes atherosclerosis is based on the experiments performed by Astrup, Kjeldsen and their collaborators.[114-123] An examination of the 38 articles published by them from 1967 to 1975 indicate that their experiments did not involve inhalation of cigarette smoke but of carbon monoxide in rabbits[124-134] and in human subjects. Atherosclerosis could not be demonstrated in man but was demonstrated only in rabbits that were fed a high cholesterol diet and in castrated male rabbits.[135-151] In their review articles, Astrup and Kjeldsen have transposed their results on carbon monoxide inhalation to cigarette smoking failing to mention that almost all attempts by

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other investigators have failed to induce atherosclerosis in animals exposed to carbon monoxide or cigarette smoke inhalation, or to nicotine injection.

This section reviews the experimental investigation according to animal species. The positive results of experimental investigation by Astrup and Kjeldsen and their collaborators are discussed together with the contradictory results of others.

1. Rabbits.

Although there are ten articles by Astrup, Kjeldsen and their collaborators on experimental atherosclerosis in the rabbit, there appears to be some repetition in that the same group of rabbits are described in two or more publications.

There are three types of exposures with the following experimental observations:

Procedure	COHb Saturation	
rabbits fed with cholesterol	15 to 20% for 5 weeks	heart displayed focal degenerative changes and scattered hemorrhages[114]
		atherosclerotic lesions and changes in lactate dehydrogenase patterns in aortic arch[115]
rabbits, male and castrated	11% for 3 months	focal degenerative changes in vascular intima and heart[119]
	16-18% for 2 weeks	ultrastructural intimal changes[120] and myocardial changes[122]

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In addition to the above, there are single exposures to 180 ppm carbon monoxide lasting for four hours producing microscopic lesions in the aortic intima and the heart.[121, 123]

The above experiments are the basis for the repeated statements by Astrup and Kjeldsen that low levels of carbon monoxide produce lesions in the heart and aorta. The lesions were seen by visual inspection only in the cholesterol-fed rabbits. The changes seen in non-cholesterol-fed rabbits were seen only under the light or electron microscope. There is a conspicuous absence of measurements of cardiac function, aortic blood pressure and organ blood flow to determine if the observed histological changes are disease processes or simply experimental artefacts that are of transient nature.

Other investigators have failed to notice any histopathological or functional changes in rabbits exposed to carbon monoxide in levels even exceeding the concentration used by Astrup, Kjeldsen and coworkers. Truhaut et al.[152, 153] did not find any alterations in the electrocardiogram or in blood pressure after 3 months exposure to 250 ppm of carbon monoxide. Andersson did not observe any change in the electrocardiogram in rabbits exposed for 14 months to carboxyhemoglobin levels ranging from 15 to 40%.[154] Birnstingl et al.[155, 156] reported aortic lesions only if rabbits were fed with cholesterol and when exposed to carboxyhemoglobin levels of 18 to 25% for 6 months.

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Although injections of nicotine cause elevation of free fatty acid levels in the blood of rabbits,[157] the experiments that relate directly to cigarette smoke

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do not show the development of atherosclerosis. Fisher et al.[158] exposed rabbits to cigarette smoke, daily for 11 to 13 months. The exposure failed to affect quantitatively or qualitatively atherosclerosis of the aorta, and coronary arteries, even in cholesterol-fed rabbits. The coronary angiograms were not influenced in rabbits exposed to cigarette smoke. The results of Fisher are significant in that they exclude any role of carbon monoxide in cigarette smoke in the pathogenesis of experimental atherosclerosis.

2. Mice, Rats, Hamsters and Dogs.

Chronic exposure in a chamber to low levels of carbon monoxide does not cause atherosclerosis in mice[159-162] and rats.[163-172] In the latter species, although nicotine administration[173,174] or cigarette inhalation[175] decreases lipoprotein lipase and elevates free fatty acid in the blood, arterial lesions could not be demonstrated. In hamsters, chronic inhalation of cigarette smoke did not produce vascular lesions morphologically comparable to human atherosclerosis.[176,177]

Wehner et al.[178] observed that smoke-exposed hamsters lived significantly longer than sham-exposed controls. They explained their results by proposing that cigarette smoke retards amyloidosis which is a frequent cause of death in hamsters.

Dogs chronically exposed to carbon monoxide do not develop atherosclerosis.[179-181] Ahmed et al.[182] exposed one-year old beagles to either cigarette smoke inhalation or nicotine injection. After a period of two years, cardiac function was measured. There were no significant differences in left ventri-

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cular function and in volume. Coronary arterial obstructive disease was absent on gross and microscopic examination. The experiments in dogs have excluded the possibility that carbon monoxide and nicotine contained in cigarette smoke can induce coronary lesions and ventricular malfunction in the dogs.

3. Subhuman Primates.

Thomsen,[183] from Astrup's laboratories, exposed Macaca irus monkeys continuously (24 hours daily) to 250 ppm of carbon monoxide with mean carboxyhemoglobin values of 20.6%. After two weeks of continuous exposure, the monkeys were sacrificed without any measurements of cardiac function. The examination of the coronary arteries showed flattening of the endothelial and subendothelial spaces which Thomsen interpreted as the initiating lesion in the development of atherosclerotic vascular disease. It is this experiment that Astrup and Kjeldsen cite as evidence that carbon monoxide contained in cigarette smoke promotes the development of atherosclerosis in man.

One observation by Thomsen[183] questions the relevance of continuous carbon monoxide inhalation to cigarette smoking. Monkeys that were exposed intermittently (12 hours on and 12 hours off) did not show vascular intimal lesions. Since smoking simulates the intermittent situation, it is not justified to transpose the results of continuous carbon monoxide to the human situation.

There are two other groups of investigators who reported a positive role of chronic exposure to carbon monoxide in the pathogenesis of atherosclerosis.

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Webster and Clarkson[184] used squirrel monkeys fed with cholesterol and De Bias et al.[186-190] used cynomolgus monkeys exposed continuously, 23 hours daily. The criticism raised above applies to these experiments, i.e. the irrelevance of continuous exposure to the smoking situation and the fact that cholesterol-fed animals behave differently from those that are not cholesterol-fed. In any event, low levels of carbon monoxide can be excluded as causing atherosclerosis on the basis of the following: Eckardt et al.[185] exposed cynomolgus monkeys 24 hours daily for two years to carboxyhemoglobin levels of 6 to 8%. These elevated levels did not lead to cardiac fibrosis, vascular lesions and brain pathology after two years of exposure, a period considerably longer than the 6 months used by De Bias et al.,[188] 7 months by Webster and Clarkson[184] and two weeks by Thomsen.[183] If all these results are interrelated, it appears that, in subhuman primates, continuous exposure to low levels of carbon monoxide produces changes in the blood vessels initially which disappear after one or two years or less.

The fundamental question as to the role of carbon monoxide in cigarette smoke can be answered as follows: In subhuman primates, the vascular effects of continuous exposure to carbon monoxide disappear after several months, and are absent during intermittent exposures. Although nicotine alone can cause experimental deposition of triglycerides in isolated arteries,[191, 192] experiments in vivo do not show experimental altherosclerosis by injection of nicotine alone.[193]

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4. Human Subjects.

The colleagues of Astrup have supplied the following observations in man to support his thesis that carbon monoxide causes atherosclerosis. Exposure to carbon monoxide increases the rate of transcapillary escape of albumin[194] and decreases the oxygen affinity of hemoglobin.[195] The relevance of these observations to atherosclerosis is based on several assumptions which have been disproven in man. First, the effects of carbon monoxide on the blood are not necessarily the same as those of cigarette smoking, for instance, on the fibrinolytic activity of whole blood, platelet adhesiveness and lipolysis.[196, 199, 200] Secondly, in the perfused human coronary artery, carbon monoxide did not influence cholesterol synthesis although it increased cholesterol uptake, whereas, nicotine increased synthesis but not the uptake.[197, 198] These observations show the difference between nicotine and carbon monoxide and raise the possibility that the two together may interact, nicotine blocking the effect of carbon monoxide on the uptake, and carbon monoxide blocking the effect of nicotine on synthesis of cholesterol. If this interaction occurs in vivo, then a combination of nicotine and carbon monoxide in the proper proportion would be expected to have no effect on cholesterol deposition in the vessel wall.

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E. Design of Future Experiments

This section has reviewed the investigations in man and animals that have been used to support the hypothesis that carboxyhemoglobin levels in cigarette smokers are high enough to cause coronary heart disease. The limitations of

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the experimental observations are discussed above and can be summarized as follows: The results are based on the inhalation of carbon monoxide which is administered either at low levels continuously, or at high levels for brief periods. Most experiments consist of carbon monoxide administration alone. In the few experimental observations that either nicotine or cigarette smoking per se has been used, the results are different from those of carbon monoxide alone.

In the future, it is necessary to realize the shortcomings of the experimental observations that have thus far been reported to examine the cardiovascular effects of carbon monoxide contained in cigarette smoke. If at all possible, the design of investigation must include an attempt to vary the carboxyhemoglobin level associated with cigarette smoking. This is difficult to execute because smokers maintain a constant level of carboxyhemoglobin regardless of the concentration of carbon monoxide in the cigarette smoke (Chapter 2).

It could be done.

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Chapter 4

CENTRAL NERVOUS SYSTEM

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Since lethal amounts of carbon monoxide cause loss of consciousness, there has been a tendency to characterize low levels of carbon monoxide as causing depression of the central nervous system. The threshold level that can exert depression has been difficult to determine. There are several tests of human performance which produce varied results. There are several animal species that have been used also with varying sensitivity to carbon monoxide. Almost all attempts to determine effects of low levels of carbon monoxide have been designed to relate to occupational exposure or environmental ambient content of carbon monoxide. The exposure consists of 8 hours a day, or continuously for 24 hours daily.

The results of prolonged exposure are relevant to establishing the occupational standard and ambient air quality standards for carbon monoxide. However, their relevance to cigarette smoking should be questioned. Since the cigarette smoker is not continuously inhaling cigarette smoke, there is no fixed sustained level of carboxyhemoglobin in a smoker. Furthermore, the levels among smokers are varied, the majority of them ranging between 2 to 8%, with some even reaching 15%. Regardless of variability, it is possible to generalize and formulate the answers to the following questions: Will smokers with carboxyhemoglobin levels as high as 15% suffer from the effects of carbon monoxide? What is the threshold level that does not influence human behavior? According to the experiments that have been properly designed

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and executed, 20% carboxyhemoglobin is the top level of 8-hour exposure that does not affect functional tests of the central nervous system. Almost all smokers show levels considerably less than 20%.

In the consideration of the effects of cigarette smoking on the central nervous system, the pharmacological actions of nicotine are usually ignored. This chapter discusses this subject and points to the beneficial effect on the central nervous system of this possible antagonism between carbon monoxide and nicotine.

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A. Inhalation of Low Levels of Carbon Monoxide Independent of Complexities of Cigarette Smoke

Until 1970, there was considerable confusion concerning the effects of low levels of carbon monoxide on the human performance of psychomotor tests.[1] Since then there has been additional investigation showing that there is no significant depression of the central nervous system at carboxyhemoglobin levels of 20% or less. The results that show negative effects at 20% or less are separated from those which show a depression.

1. No Effect on Human Performance at 20% or Less.

The first investigation of the effects of carbon monoxide on human performance was performed by Forbes et al.[2] in 1946. They tested 8 normal men on their performances in simple tests of reaction times, binocular vision, co-ordination of the hand and eye. The results of these tests were unaffected by breathing carbon monoxide until their blood was 30% saturated. There was slight impairment in their performance at 45% saturation. Subsequent work has confirmed a lack of effect with levels up to 20% and that levels higher than 20% caused impairment of visual function and manual coordination.

a. Stewart and his collaborators. Human volunteers were exposed to carbon monoxide in concentration of 1, 25, 50, 100, 200, 500 and 1000 ppm for periods of one-half to 24 hours. Exposures producing carboxyhemoglobin saturations greater than 15 to 20% resulted in delayed headaches, changes in

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visual evoked response and impairment of manual coordination. However, levels up to 15 and 20% did not influence the performance testing in time estimation, reaction time, steadiness, manual dexterity, the electroencephalogram and the visual evoked response.[3] The ability to perceive time was not impaired in a range of carboxyhemoglobin saturations of up to 20%.[4,5]

b. Mikulka, O'donnell and their collaborators.[6-9] Human subjects were exposed to 0, 50, 125, 200 and 250 ppm of carbon monoxide for 3 hours. With carboxyhemoglobin levels as high as 12.4%, there were no significant symptoms reported by the subjects. There was also no overall trend toward poorer estimates of 10-second interval and no deterioration of tracking performance. The subjects were also exposed to 75 and 150 ppm of carbon monoxide during sleep for 9 hours. With levels of 5.9 to 12.7% carboxyhemoglobin saturation upon waking, the subjects did not show performance decrements in mental arithmetic, time estimation, tracking, monitoring and visual tests.

2. No Effects on Human Performance at 10% or Less.

a. MacFarland and collaborators.[10-20] The first study reported in 1944 showed that exposure of subjects to carbon monoxide mixtures of up to 20% carboxyhemoglobin influenced vision. There was an impairment in visual threshold when the saturation reached 4 to 5%.[10] In a 1973 study, subjects were exposed to 700 ppm of carbon monoxide until carboxyhemoglobin levels of 6%, 11% and 17% were reached.[20] The subjects were tested as to their

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ability to perform both selected driving-related laboratory tests of visual response and control reactions and over-the-road vehicle driving. Compared to the test results prior to exposure to carbon monoxide, the 6% carboxyhemoglobin level had no effect on driving ability. The 11% and 17% carboxyhemoglobin levels did not appear to seriously affect the ability to drive motor vehicles although there were some statistically-significant differences in some of the tests suggesting some decrement in performance. The earlier results of MacFarland et al. of visual impairment when saturation reached less than 10% has not been confirmed by their recent studies.

b. Guest and collaborators.[21] Eight healthy subjects were exposed to a mixture of carbon monoxide in air to raise carboxyhemoglobin saturations to 10%. In a double-blind study, the exposure did not depress the auditory flatter fusion and critical flicker fusion thresholds. In the same subjects, the oral administration of pentobarbital caused the expected depressant effect on both thresholds.

c. Hanks. Critical tracking task test was used by Hanks in subjects exposed to 0, 25, 50, 75 and 100 ppm for up to 4 1/2 hours. With carboxyhemoglobin levels up to 10%, there was no change in performance of the critical tracking task test.[22]

d. Rockwell and collaborators.[23-25] In four series of experiments in-

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volving 25 human subjects, the exposure to carbon monoxide up to 20% carboxyhemoglobin saturation had the following effects on driving-related tasks. There was no change in gross and fine manual coordination, nor in spatial relational abilities. However, there was a decrease in blink rates and an increase in tracking-lag errors.

3. Effects on Human Performance Below 10%.

The investigators who describe a reduction in human performance even when carboxyhemoglobin levels are below 10% are as follows: Beard and his collaborators who initially reported an influence in performance,[26-29] later denied confirming their results when performed double-blind.[30] The results of Horvath et al.,[31] Schulte,[32,33] Bender et al.,[34,35] Fodor and Winneke,[36] Wright et al.[37] and Groll-Knapp et al.[38] have been disproven by the work discussed above using similar techniques.

4. Electroencephalogram in Man.

Hosko[39] failed to observe any change in the spontaneous electroencephalogram in human subjects exposed to carbon monoxide up to 20%. Grudzinska and Pecora[40] did not report any abnormalities in the electroencephalogram in 60 workers exposed in their work environment to carbon monoxide levels with 5 to 20% carboxyhemoglobin levels. The recording of the electroencephalogram indicates that levels below 20% carboxyhemoglobin do not influence the central nervous system.

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B. Cigarette Smoking

If the carbon monoxide contained in cigarette smoke would influence the central nervous system of the smoker, supportive evidence can be derived by subjecting the same group of subjects to carbon monoxide inhalation and then, to cigarette smoking using the same performance tests described above (see A above). Such a comparison has not been completed. The results relating to cigarette smoking only show signs of stimulation as well as depression of the central nervous system depending on the manner of detection of nervous activity.

1. Electroencephalogram and Sensory Perception.

Philips used computer analysis of electroencephalographic data recorded during resting and working conditions.[41] The effects seen immediately after smoking cigarettes indicate increased alertness, accompanied by facilitation of responses to repeated visual stimulation. The results are significant in that they represent the total response of the central nervous system, confirming the stimulant action of nicotine seen in animals (see C below).

The smoking of cigarettes did not influence the following tests on the eye: pupillary size and glare recovery time,[42] ability to detect objects in simulated night driving conditions,[43] flicker fusion threshold,[44] electroculogram[45] and intraocular pressure.[46] There are reports of transient reduction in peri-

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pheral field of vision following cigarette smoking[47-50] but Krippner and Heimstra[50] question the functional importance of static peripheral activity, i.e. it is not known whether man receives and makes use of static peripheral visual information in dealing with his environment. The same question applies to reported depression of electromyogram[51] and of the patellar reflex seen in smokers.[52]

Differential sensitivity of taste, odor and touch is not significantly different between smokers and nonsmokers.[53] The reported impairment in hearing and reduced pain tolerance seen in smokers compared to nonsmokers[54-59] does not necessarily mean that smoking is the cause of the difference. Seltzer and his collaborators[58, 59] have suggested constitutional differences between smokers and nonsmokers as a possible explanation for the effect of smoking on pain perception and hearing loss seen in adult smokers.

2. Performance Tests.

The influence of cigarette smoking was investigated by three groups of investigators who failed to detect any change in the following tests: tracking and loading tasks conducted by Schori and Jones,[60, 61] simulated driving task by Heimstra et al.[62, 63] and manual dexterity and response time performance by McCune.[64] Cigarette smoking increased arousal which is accompanied by tachycardia.[65-68] Andersson[68] showed that retention of learning was better in the smoking condition than in the nonsmoking condition. Although reaction

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time is shortened 5 min after smoking, the test was significantly faster 40 min and 55 min after smoking, compared to the control measurement before smoking.[69] The biphasic effect of smoking is seen also in animal experiments described in the next section.

C. Interactions Among Carbon Monoxide, Nicotine and Other Drugs

Thus far, this chapter has been reviewing the effects of carbon monoxide separately from cigarette smoking in human performance. The interactions between nicotine and carbon monoxide cigarette smoke have been alsmot entirely ignored by the investigators who have been examining either carbon monoxide alone (see A) or cigarette smoking (see B). Since lethal concentrations of carbon monoxide cause depression of the central nervous system, and lethal injections of nicotine cause convulsions, it is reasonable to suspect that sublethal amounts of both would be antagonistic. A review of the literature indicates that antagonism has been demonstrated by a few techniques in some animal species including man. However, attempts tc detect chemical interaction in man are difficult to perform because of complicating factors which are discussed below.

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1. Interactions in Man.

Weber et al. have recently demonstrated that the results of physiological

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functions depend on the degree of activation of the subjects.[70] They examined the effects of low carbon monoxide exposure on the critical flicker fusion technique. In a monotonous situation, carbon monoxide inhalation caused a reduction in test values whereas in an activating situation, the values remained unchanged.

Cigarette smoking and nicotine exert either a stimulation or a depression depending on the mood of the subject; sedation when excited and stimulation when depressed.[71,72] An interaction between carbon monoxide and nicotine will be difficult to detect because of the change in mood of the subject that determines the reaction to the experimental situation. A primary action elicits a secondary action so that identification of the individual effects of carbon monoxide and nicotine will require a complex protocol of experimentation.

a. Carbon monoxide and nicotine. Vestibular nystagmus (lateral movement of the eye during rotation of the body) has been examined by Tibbling to determine any influence of the components of cigarette smoke.[73] She compared the effect of cigarette smoking with intravenous injection of nicotine and smoking of a "nicotine-free" cigarette. However, the subjects were not exposed to carbon monoxide mixture to determine any change in frequency of nystagmus. Her conclusion that nicotine alone is responsible for increase in frequency of nystagmus has not excluded the possibility that carbon monoxide has the opposite effect.

The electroencephalographic changes related to smoking would be a way

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of determining interaction between nicotine and carbon monoxide. However, Hauser et al.[74] noted similar changes in the electroencephalographic pattern while the subject smoked a cotton-filled glass cigarette. The change in dominant frequency of the electroencephalogram has more to do with the act of smoking than any changes due to substances present in the cigarette.

b. Cigarette smoking and caffeine. The effects of caffeine and cigarette smoking on the central nervous system are similar in man. Ashton et al.[75,76] measured the negative shift in the vertex electroencephalogram which occurred prior to an expected stimulus. Both caffeine and cigarette smoking increased the magnitude of the negative shift. Unfortunately, the test did not extend to nicotine or carbon monoxide to determine interaction. The similarity of effects of caffeine and cigarette smoking may help explain the recent observation by Kozlowski[77] that coffee-drinking cigarette smokers take in more nicotine when they reduce their intake of caffeine. However, as the dose of caffeine increases, there is no reduction in nicotine intake. Coffee-drinking cigarette smokers are still able to discriminate between caffeine and nicotine.

Gramberg-Danielsen et al.[78] described another similarity between caffeine and nicotine. Measurements of twilight vision, glare sensitivity and readaptation time are influenced by smoking of cigarettes and by caffeine. There is no information whether or not there is an additive effect of both. There is the possibility that the carbon monoxide contained in cigarette smoke would

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antagonize the effect of caffeine, an interaction that has been demonstrated in animals (see below).

2. Subhuman Primates.

The intravenous injection of nicotine in the squirrel monkey produced an arousal state in the electroencephalogram which is closer to a normal arousal than that induced by caffeine.[79] This technique of recording arousal electroencephalogram would have been ideal to show interaction between inhalation of carbon monoxide and inhalation of cigarette smoke. The exposure of macaca monkeys to 200 ppm carbon monoxide continuously for 100 days did not influence the performance tests.[80,81] The monkeys tolerated 22% carboxyhemoglobin saturation continuously for 100 days, thus verifying the conclusion in man that 20% does not influence the central nervous system.

3. Cats.

Brown and Shryne[82] observed an alert pattern in the electrical activity of the unanesthetized cat following the subcutaneous injection of nicotine. The effects of nicotine, carbon monoxide and cigarette smoke were similar on cortical recordings of the isolated perfused head preparation.[83-85] The responses consisted of cortical activation, behavioral arousal and vasodilation of cerebral blood vessels.

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4. Rats.

Nelsen and Goldstein[86] trained rats on an attention task which required

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them to respond with a single lever press to a very short, variably-presented stimulus for food reinforcement. Treatment with nicotine caused improvement in performance. Morrison and Stephenson[87] observed an improvement in lever-pressing performance in rats treated with nicotine. In his own series of experiments, Erickson[88] concluded that nicotine facilitated the consolidating neural memory trace.

On the other hand, inhalation of carbon monoxide depresses the performance of rats. The threshold exposures that did not influence the central nervous system are as follows: 200 ppm for two hours on reinforced performance,[89] 100 ppm continuously for four days on sleep and waking pattern.[90] Although the effects of higher concentration of carbon monoxide can be antagonized by carbon dioxide,[91] an interaction with nicotine has not been tested.

5. Other Species.

There are reports of stimulant action of nicotine and depression by carbon monoxide in mice,[92-95] rabbits,[96-99] guinea pigs,[100] and pigeons.[101] The dosages of the stimuli and the type of behavioral effects are of such a nature that it is difficult to judge the relevance of the results to humans. The animal experiments did not include interaction between carbon monoxide and nicotine.

D. Practical Aspects of Effects on the Central Nervous System

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A review of the literature reveals that depression of the central nervous system by carbon monoxide is seen only when carboxyhemoglobin levels are

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above 20%. The reports claiming a depression at levels below 10% are questionable and have not been confirmed. Since the majority of cigarette smokers has carboxyhemoglobin levels of less than 5%, a possible influence of carbon monoxide on cerebral function can be excluded. In the few smokers with levels exceeding 10%, any effect of carbon monoxide is likely to be antagonized by nicotine contained in cigarette smoke.

In recent years, there has been a tendency to exaggerate the depressant action of carboxyhemoglobin on human performance. Specifically, it has been suggested that pilots who smoke are likely to perform poorly because of the carbon monoxide contained in cigarette smoke.[102-104] The review of the literature indicates that this is not likely to occur (see A above). Furthermore, nicotine contained in cigarettes improves performance so that antagonism between carbon monoxide and nicotine would be expected to occur (see B above). Thus far, the possibility has been ignored and almost all experiments in man and animals have not been designed to check this possibility (see C above). Additional experiments are needed to test in the same preparation, nicotine, carbon monoxide and cigarette smoke in a manner that would be relevant to the human smoking problem.

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Chapter 5

PREGNANCY

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The reproductive system has been publicized as much as the cardiovascular and central nervous systems as target organs influenced by the carbon monoxide contained in cigarette smoke. Pregnant women are being warned that cigarette smoking causes low birth weight, prematurity and perinatal morbidity and mortality.

Although pregnant women who smoke have a higher incidence of low birth weight infants than nonsmokers, this association is not necessarily one of cause and effect. Since 1972, there have been additional epidemiologic studies which question a causal effect of smoking. Women who smoke are different from nonsmokers in their familial background, nutrition, socio-economic factors and environmental exposures. The details of epidemiologic and environmental studies are reviewed in this chapter, as they relate to low birth weight. Mortality and morbidity statistics of the newborn have been excluded because they are influenced by factors which are remotely related to carbon monoxide contained in cigarette smoke.

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A. Carboxyhemoglobin Levels in Pregnancy

The blood levels of carboxyhemoglobin in pregnant women are in the same range of values as in nonpregnant women. For pregnant smokers, the range of values reported by various investigators is as follows:

Investigators (year)	Number Pregnant Women	COHb % Saturation mean ± SD	(range)
Haddon et al. (1961)[1]	13		(0 - 8.4)
Heron (1962)[2]	21	6.7	(1.6 - 14)
Young and Pugh (1963)[3]	6	2.0±0.7	(1.0 - 3.0)
Younaszai et al. (1968)[4]	16	8.3	(2.0 - 12.0)
Scoppetta (1968)[5]	28	4.5	(0.5 - 15.0)
Baribaud et al. (1970)[6]	27	4.4	
Cole et al. (1972)[7]	93	4.1	(0.5 - 14.0)

The above results show a wide range of values for carboxyhemoglobin in pregnant smokers. Although the mean values are higher than those seen for pregnant nonsmokers (omitted from above table), there is an overlapping in the values for both groups.

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1. Fetal Blood.

In most of the studies on maternal blood levels tabulated above, the corresponding fetal blood has been analyzed. The % saturation in the fetal blood is higher than the maternal blood because of the lower hemoglobin values in the former.

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2. Carbon Monoxide Uptake During Smoking.

Pavlou et al.[8] obtained samples before and after smoking cigarettes. The patients showed a steady rise from 1 - 4.2% in the control period to 5.3 - 11.2% at the end of the smoking period. The duration of the change was not followed. These transient changes in the maternal blood are probably not reflected in the fetal blood because of the slow diffusion of carbon monoxide through the placenta.[9-11] The rise in carboxyhemoglobin concentration in response to smoking a single cigarette was compared in pregnant women, pregnant women suffering from anemia, and nonpregnant women. Dow et al.[12] reported the following responses to smoking:

	% CO Hb Mean ± S E		
	Before Smoking	After Smoking	Δ
pregnant (nonanemic)	1.68±0.27	5.55±0.34	3.87
pregnant anemic	1.68±0.2	6.7±0.2	5.0
nonpregnant (nonanemic)	2.24±0.2	4.3±0.19	2.11

The conclusion of Dow et al.[12] is that pregnant women, particularly those suffering from anemia, show a more-pronounced increase in carboxyhemoglobin levels than nonpregnant women. If the implication is that anemia causes an increase in uptake of carbon monoxide, that is fallacious as pointed out by Payne[13] who calculated the absolute concentration from the percentage saturation. The levels are as follows:

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	CO Hb in mg/100 l		
	Before Smoking	After Smoking	Δ
pregnant (nonanemic)	203	672	469
pregnant anemic	150	596	446

In the above table, the uptake of carboxyhemoglobin as a result of smoking by anemic pregnant women is no greater than that for nonanemic subjects. When levels of carboxyhemoglobin are expressed in terms of absolute amounts, anemia does not increase the uptake of carbon monoxide in pregnant women.

3. Effect on the Fetus.

Asmussen and Kjeldsen[14] have recently reported their observations on the ultrastructure of umbilical arteries from newborn children. They reported intimal changes seen in the arteries of children of smoking mothers which were not seen in those of nonsmoking mothers. They interpreted these differences as representing early signs of atherosclerosis, similar to those seen in rabbits exposed to carbon monoxide (see Chapter 3).

It should be pointed out that atherosclerosis is not a disease of the newborn and that the umbilical and placental arteries behave differently from the systemic arteries. Kawahara et al.[15] have compared the response of human placenta and systemic blood vessels and noted the opposite effects of vasoconstrictors and vasodilators. Furthermore, the uteroplacental blood pool does not respond in a consistent manner to cigarette smoking. Cloeren et al.[16] reported 5 pregnant women who initially showed a slight decrease followed by an increase whereas in the other five, there was only an increase in the

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uteroplacental blood pool following cigarette smoking. This variability is consistent with the proposition that smokers are not a uniform population and that the placental vessels do not behave in a uniform fashion.

4. Role of Nicotine.

There is a change in the fetal breathing movements during maternal smoking.[17] Gennser et al.[17] explain the effect as a result of nicotine that has crossed the placental barrier. Although nicotine has been detected in samples of amniotic fluid, it is not uniformly seen in all smokers. Van Vunakis et al.[18] found nicotine in 22 out of 37 samples in smokers with the following wide distribution of concentration.

No. of Smokers	Range of nicotine ng/ml/amniotic fluid
15	0 - 10
13	11 - 20
8	21 - 30
1	31 - 40

The wide range of nicotine concentration in the amniotic fluid reflects the variability of nicotine absorbed from cigarette smoke among smokers. It is unlikely that a dose response relationship can be derived from amniotic fluid levels and daily consumption of cigarettes.

B. Association of Smoking with Birth Weight

Until 1972, the epidemiologic studies indicated that smoking mothers had newborns of lower birth weight than nonsmoking mothers. The prevalent opinion expressed in the Surgeon General Reports (1967, 1969, 1971, 1972) was that smoking, particularly the elevated carboxyhemoglobin, was the cause of

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the low birth weight. The subject has been omitted from the 1973, 1974 and 1975 Reports so that recent events have not been publicized. They are as follows:

1. Examination of Future Smokers Before Acquisition of the Smoking Habit.

In 1972, Yerushalmy[19] explored the question whether "this increase in low birth weight infants to smoking gravidas is due to the smoking or the smoker". Unlike previous epidemiologic studies, Yerushalmy investigated the reproductive performance of future smokers during the periods before they acquired the smoking habit. His conclusion was that women who subsequently became smokers had a high incidence of low birth weight infants during the period before they began to smoke. He questioned the role of smoking as an exogenous factor and proposed instead that the cause of the low birth weight lies in the smoker herself. The results of epidemiologic studies since 1972 have revealed the importance of maternal nutrition which, in turn, influences fetal nutrition.[20-25] Prematurity and low birth weight are seen more frequently in the black group regardless of smoking habit.[26-28] Socioeconomic factors, education, legitimacy, familial trends, ethnic origin and age of the mother influence the perinatal mortality.[29-35] The role of smoking has not been evaluated because of the concurrent risk factors which differ between smokers and nonsmokers. The smoking habit of the father also influences the status of the newborn[36] suggesting that a genetic factor from both parents is transmitted to the offspring which, in turn, influences birth weight and perinatal morbidity and mortality. This subject is

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discussed further in Chapter 9. The original study of Yerushalmy in 1972,[19] as well as the subsequent investigations cited above, have led to an exchange of correspondence among investigators,[37-52] The major criticism revealed in published letters is that epidemiologic studies cannot support causal relationships between smoking and low birth weight.

2. Identification of Chemical Factors Influencing the Fetus.

A reduction in birth weight from chronic carbon monoxide poisoning has not been reported. There are no published epidemiologic studies of women exposed occupationally to carbon monoxide. The literature on maternal poisoning indicates death of the fetus with carboxyhemoglobin levels as low as 10% saturation in the mother.[53-61] There is reason to suspect that this level was not the highest amount of carbon monoxide exposure causing fetal death.

In recent years, several chemical factors in the environment have been suspected of causing a reduction in birth weight. They include carbon monoxide and other air pollutants,[62-64] plant constituents that are likely to be ingested,[65] high nitrate content in the water[66] and trace metals in the water, food and atmosphere.[67] Drugs such as salicylates,[68-70] diphenylhydantions,[71] caffeine,[72] alcohol[72-75] and hormones[76-81] have been reported to cause fetal malformations, prematurity and neonatal deaths. These chemical factors have not been considered in the epidemiologic investigation of risk factors (see above).

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C.: Correlation of Human Studies and Animal Experiments.

In 1972, Astrup et al.[82] reported the results of human and animal studies and concluded that the "carbon monoxide in tobacco smoke might be responsible for the reduced birth weight of babies whose mothers smoked during pregnancy." There are several features in this report which have been overlooked.

1. Variability of Carboxyhemoglobin Levels in Pregnant Women.

Pregnant women in the outpatient clinic of a hospital in Copenhagen were chosen at random and blood samples were taken for carboxyhemoglobin levels. The results indicate a considerable overlapping of values between smokers and nonsmokers:

COHb % Saturation	No. of Pregnant Women	
	Smokers	Nonsmokers
0-1%	336	678
1-2%	155	128
2-3%	139	51
3-4%	105	16
4-5%	50	7
5-6%	21	1
6-7%	11	2
7-8%	2	1
8-9%	4	0
9-10%	1	0
Total	824	884
Mean COHb	1.92%	0.87%

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Although the distribution of carboxyhemoglobin values was tabulated, only the mean values for birth weight were mentioned: 2990 g for smokers and 3225 g for nonsmokers. They further stated that, among smokers, there was a "negative correlation between birth weight and mean value of carboxyhemoglobin measurements of each individual."

Astrup et al.[82] did not mention the correlation of birth weight with carboxyhemoglobin measurements of nonsmokers. In the discussion of their results, they were oblivious to the considerable literature on the role of risk factors, particularly of nutrition which was called to their attention by Neale.[83] Subsequent to 1972, the report of Yerushalmy[19] and others appeared invalidating the premise of Astrup et al. that smoking was the cause of the low birth weight.

2. Rabbit Experiments on Carbon Monoxide by Astrup et al.

Astrup et al.[82] exposed rabbits to carbon monoxide continuously for 30 days, from mating until the day before expected delivery. The rabbits that had concentrations of 16 to 18% had 35% stillbirths and offspring which died within the first hour, and lower birth weight than control rabbits. Since the levels of 16 to 18% were never attained in Astrup's patients, these experiments are irrelevant to the human studies.

The next exposure experiments by Astrup et al.[82] consisted of rabbits exposed continuously to carboxyhemoglobin levels of 8 to 9 %. Again, this level was seen only in one out of 824 pregnant women. Astrup et al. did not

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report animals exposed to levels of 5% carboxyhemoglobin saturation, which would be relevant to their observations.

3. Experiments by Other Investigators.

Although Astrup et al.[82] reported the results of their rabbit experiments in 1972, there has been no confirmation of their results. To the contrary, there are observations which question the relevance of carbon monoxide experiments to the smoking question. Kirschbaum et al.[84] injected nicotine and administered cigarette smoke to pregnant ewes. Gas exchange and cardiovascular function were unchanged in both the ewes and their fetuses. Chronic exposure to cigarette smoke in mice[85] and rats[86] that were pregnant did not influence birth weight nor induce malformations of fetuses. The experiments showing a reduction in birth weight of newborns of rats exposed to cigarette smoke are explained by a reduction in food intake by the pregnant rats.[87]

D. Practical Aspects of Smoking in Pregnancy

That smoking during pregnancy causes an elevation in carboxyhemoglobin level and reduction in birth weight of the newborn is not supported by experimental and epidemiologic data and indeed is rejected by better-designed studies. Animals exposed to cigarette smoke do not duplicate the results of exposure to carbon monoxide. Furthermore, there is a considerable degree of overlapping of carboxyhemoglobin levels of smoking and nonsmoking women in pregnancy.

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Several risk factors in pregnancy have been identified as contributing to the low birth weight of infants of smokers, such as their familial background, nutritional status, socioeconomic factors and environmental exposure to chemicals.

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Chapter 6

WORKERS EXPOSED TO CIGARETTE SMOKE AND STATIONARY SOURCES OF CARBON MONOXIDE

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This chapter discusses the subject of carboxyhemoglobin levels and the diseases associated with carbon monoxide exposures discussed earlier (see Chapters 2, 3 and 4). The central theme in this chapter is the influence of cigarette smoking on workers who are also exposed to stationary sources of carbon monoxide in their work environment. The problem is a complex one because the diseases that develop in these workers are usually related to their occupation. It is difficult to evaluate the sources of carboxyhemoglobin, namely carbon monoxide in the work environment, carbon monoxide from metabolism of a chemical used by the worker, and carbon monoxide from cigarette smoking. In the epidemiologic comparisons showing that the incidence of cardiovascular disease has a positive correlation with carboxyhemoglobin levels (Chapter 3), the differences in occupational exposure were not taken into account. The same criticism applies to the association between carboxyhemoglobin levels of mothers and low birth weight of their offspring (Chapter 5). This chapter discusses the carboxyhemoglobin in workers to illustrate the importance which occupational exposure could have if such exposures could be causally related to diseases of the cardiovascular and bronchopulmonary systems.

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A. Exposure to Carbon Monoxide

It is important to discuss the group of workers who are positively exposed to carbon monoxide. These workers have elevated levels of carboxyhemoglobin and develop signs of acute poisoning. However, the long-term effects of carbon monoxide in workers is difficult to prove because of the concurrent exposure to other inhalants.

1. Firemen.

One major stationary source of carbon monoxide is the accidental combustion of houses and buildings. Sammons et al.[1] investigated Oklahoma City fire fighters to determine whether they had residual elevated levels of carboxyhemoglobin following occupational exposure. A control group was paired for age, weight, race, smoking habits and family history of cardiovascular and pulmonary disease. The blood samples were taken monthly for 5 months. The nonsmoking fire fighters had a mean level of 5% saturation, whereas the nonsmoking controls had a mean level of 2.3%. As a group, the fire fighters exhibited changes in enzyme activities in the blood that suggest myocardial damage.

A group of 13 fire victims showed levels of 8 to 40% with signs and symptoms of carbon monoxide poisoning: headache, weakness, confusion and restless behavior.[2] In another group of four victims, there was lactic acidemia associated with carbon monoxide poisoning.[3]

Peters et al.[4] studied the pulmonary function in 1,430 Boston fire fighters during the period of 1970 to 1972. The rate of loss in pulmonary function

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observed for the entire population was more than twice the expected rate. The reductions in forced vital capacity were significantly related to frequency of fire exposures and could not be explained by differences in age, smoking habits or ethnic background. The results of this study indicate the contribution of exposure to products of combustion in the impairment of pulmonary function in fire fighters.

In a recent abstract, Kurt and Peters[5] examined the cardiac risks of the same group of fire fighters in Boston. The levels of carboxyhemoglobin were reported to be as high as 17.8% saturation. There were coincident abnormalities in serum lipids and the electrocardiogram which could not be explained by carboxyhemoglobin levels.

Firemen are exposed not only to carbon monoxide but also to products of combustion. The carbonization of plastics is a primary source of carbon monoxide. The other products of combustion have been examined acutely in animals resulting in pulmonary lesions.[6-10] There are no chronic exposure experiments to show development of heart disease. The survivors of a 1929 fire at the Cleveland Clinic were examined in 1965.[11] On the basis of the data collected, it was not possible to detect any long-term effects on the mortality experience of survivors with known exposure to carbon monoxide and other gases produced by the decomposition of nitrocellulose x-ray film at the Cleveland Clinic fire.

2. Steel Workers.

In 1929, Farmer and Crittenden[12] examined the blood of steel mill operators at the end of a working day, again, in the morning as they reported for work and finally at the end of the second working day. Their results were

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as follows:

	Mean % COHb
First day 4:00 p.m.	6.26
Second day 8:00 a.m.	2.11
Second day 4:00 p.m.	7.01

The increase in carboxyhemoglobin levels in the course of a working day noted above has been confirmed by Jones and Walters,[13] Schieche et al.,[14] and Alvarez de Lugo[15] and Crosetti et al.[16] The most recent study was reported in 1974 by Butt el al.[17] who measured carboxyhemoglobin levels at the beginning and end of a single, work shift. A hundred blast furnace workers and a randomly-selected control group of 87 men with no occupational exposure to carbon monoxide were tested over a five-day period. The results permitted the comparison of smokers and nonsmokers before and after occupational exposure.

a. Beginning of shift. There were six groups differentiated according to their smoking habits, three control groups and three groups working at the blast furnace.[17] The mean and Standard deviation for each group of 21 to 45 subjects were as follows:

Categories	COHb %: mean ± S.D.	
	Control	Blast Furnace
nonsmokers	0.9 ± 0.32	1.1 ± 0.46
smokers (<20/day)	3.3 ± 1.45	2.9 ± 2.01
smokers (>20/day)	5.0 ± 2.25	6.0 ± 2.80

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The above values show a standard deviation for smokers that is five to seven times larger than that for nonsmokers, both control groups and working groups. The values for nonsmokers overlap with those of the smokers indicating the considerable range of values for smokers (see Chapter 2).

b. End of shift. For the blast furnace workers, the increase of carboxyhemoglobin levels was as follows:[17]

blast furnace	Δ of Mean before and after shift
nonsmokers	2.9
smokers (<20/day)	2.1
smokers (>20/day)	2.5

The mean uptakes of carbon monoxide for smokers are lower than that of nonsmokers. These results can be interpreted to mean that when smokers are exposed to occupational sources of carbon monoxide, their net uptake is less than that of nonsmokers (see also Chapter 1).

3. Welders.

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Carbon monoxide is absorbed by welders in the course of their work. De Kretser et al.[18] measured carboxyhemoglobin levels in 60 welders and reported a range of 0 to 20%. After improving ventilation, there was a reduction to a range of 0 to 10%. Smoking cigarettes had no influence in the carboxyhemoglobin level of this group of welders. The opinions that smokers have higher levels than nonsmokers expressed by Cascini and Gazzerro[19] and by Brigatti et al.[20]

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are not based on data derived from welders.

B. Diseases Associated with Occupational Exposure to Carbon Monoxide

Most workers exposed to levels above 200,000 ppm of carbon monoxide die after a few minutes of exposure.[21-23] Those who lose consciousness and recover from the poisoning may show some residual effects on the central nervous system,[24] and a few cases reports show cardiac injury with electrocardiographic abnormalities.[25-29] Most of these reports on carbon monoxide poisoning were on workers exposed directly to gas containing carbon monoxide[21-29] or to smoke.[30]

The question of long-term exposure of workers to carbon monoxide is more difficult to answer. In contradiction to the theory that a low level carbon monoxide in the work environment is dangerous to the heart, the mortality studies of gasworkers[31] and steelworkers[32] do not show a high incidence of death from heart disease (see Chapter 3).

C. Occupational Exposure Not Involving Carbon Monoxide

Although there is no disease syndrome associated with occupational exposure to low levels of carbon monoxide, there are diseases known to occur

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with prolonged exposure to chemicals, dusts and particulate matter. It is important to briefly mention these occupational diseases because they are likely to appear in nonsmokers as well as in smokers. There is no data to indicate that smokers are more susceptible than nonsmokers to the following occupational diseases.

1. Chlorinated Solvents that are Metabolized to Carbon Monoxide.

Prolonged exposure to low levels of chlorinated solvents cause hepatotoxicity.[33] Dichloromethane (methylene chloride)[34, 35] and dibromomethane[36] are metabolized in the body to carbon monoxide, a phenomenon that is seen only for these two solvents. So far, the health hazard of the formation of carbon monoxide in vivo has not been fully appreciated. Smokers exposed to either chlorine gas or ethylene do not show differences in lung function compared to nonsmokers.[37, 38]

2. Hypersensitivity Reactions.

The list of substances that cause hypersensitivity or allergic response in workers has been increasing in number. The manifestations are usually in the respiratory system and are usually diagnosed incorrectly as chronic bronchitis. The substances that cause allergy of the respiratory tract of workers are as follows:

gasoline[39]

propionates[40]

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insecticides[41]

enzymes for detergents[42-44]

coffee powder[45]

grain dust[46-48]

grain weevil[49]

moldy hay and moldy vegetable produce[50, 51]

fungus[52]

bird excreta and dandruff[53]

wood dust[54]

mine dust[55]

woll dust[56]

chimney dust[57]

flour and baking soda[58]

To the above list, tobacco dust can be added. Tobacco workers develop dermatitis.[59-61] Valic et al. examined the respiratory responses of 318 nonsmoking female workers in 3 cigarette factories in Yugoslavia.[62] The prevalences of chronic bronchitis and nasal catarrh were not higher among subjects exposed to tobacco dust than among the control group. A significant temporary decrease in ventilatory capacity during the work shift was recorded among the nonsmoking women. The mechanism of the reduction was not discussed. The effect is probably caused by the inhaled dust per se independent of the nicotine contained in the tobacco.

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D. Practical Aspects of Occupational Exposure to Carbon Monoxide

An examination of the literature on occupational exposure of cigarette smokers indicates that, at the present time, it is difficult to identify the cause of their diseases. Some of the respiratory problems are more likely to be attributed to the work environment, such as the chemicals and dust particles which induce hypersensitivity in the workers. The carbon monoxide in the work place causes an elevation of the carboxyhemoglobin level but there is no evidence that low levels cause cardiovascular disease.

The occupational standard for carbon monoxide is under consideration by the Occupational Safety and Health Administration. The level of 50 ppm in force in the United States[63] is being questioned. A standard of 35 ppm carbon monoxide is suggested based on the reported effects of low levels of carbon monoxide on the heart and on the central nervous system, the subject covered in Chapters 3 and 4.[64] There is a definite impression that the proposed standard of 35 ppm which is calculated to keep the carboxyhemoglobin level of workers at 5% will force the dismissal of some workers who are now employed in areas containing sources of carbon monoxide. The carboxyhemoglobin levels of smokers vary substantially from individual to individual, and from day to day and from hour to hour (see Chapter 2). Those

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who exceed 5% carboxyhemoglobin because of the nature of the uptake and elimination of carbon monoxide will suffer from unemployment. Both smokers and nonsmokers who live in areas with high levels of carbon monoxide in the ambient air as well as those exposed to vehicular traffic will be excluded by the proposed standard. The new proposal has stirred a considerable amount of controversy among authorities.[65-70] Additional investigation is needed to determine the justification for changing the occupational standard to 35 ppm carbon monoxide.

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Chapter 7

CIGARETTE SMOKE AND MOVING SOURCES OF CARBON MONOXIDE

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The carboxyhemoglobin contained in the blood of smokers originates, in part, from the carbon monoxide emitted by vehicular engines. The proportion of the total carboxyhemoglobin originating from moving sources of carbon monoxide varies from individual to individual depending on the extent of exposure. Those who are inside the moving vehicle are likely to be exposed to the highest concentration of vehicular emission, specially if the vehicle is not properly ventilated with ambient air and the inflow into the vehicle contains a high concentration of the engine exhaust. Workers in garages and tunnels, although outside the vehicle, are in an environment that is partly enclosed preventing free elimination of the vehicular emission into the ambient air. The exposure levels of carbon monoxide of garage men and tunnel inspectors are higher than those of policemen and pedestrians in open areas such as street intersections during hours of heavy traffic .

Smokers with carboxyhemoglobin levels originating from exposure to vehicular carbon monoxide have been compared with nonsmokers. The differences in their health status have been explained by cigarette smoking alone although other variables have not been controlled. The extent of exposure to vehicular traffic is difficult to match between smokers and nonsmokers. The composition of vehicular emission is so complex that a comparable exposure even for a specified group of workers is difficult to attain. The concentration of sulfur dioxide, nitrogen oxides, carbon monoxide and particulate matter vary continuously at various locations and in the same location at different times

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of the day. Smokers and nonsmokers exposed to vehicular emissions are likely to suffer from the involuntary inhalation of pollutants.

A. Exposure Inside Vehicles

Most studies relate to automobiles, although there are a few on buses, moving trains, ferry boats and air planes. It is not practicable to apply results from one vehicle to other forms of vehicles because of the differences in size of the engine, the number of passengers and the degree of ventilation.

1. Carbon Monoxide Levels Inside Vehicles.

a. Automobiles. The concentration of carbon monoxide inside motor vehicles has been reported from various states and countries. Goldsmith and Rogers[1] reported the levels inside the driver's compartments in 1,105 California vehicles. Although 92% of the vehicles had levels below 50 ppm, the remainder had concentrations of 50 to 650 ppm. Brice and Roesler[2] reported the following half-hour integrated samples at the following cities:

	No. of Vehicles	Carbon Monoxide ppm mean (Range)
Chicago	16	37 (20 - 50)
Cincinnati	145	21 (8 - 50)
Denver	28	40 (22 - 72)
St. Louis	47	36 (11 - 77)
Washington	44	25 (7 - 43)

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In all cities, 75% of the samples taken inside moving vehicles were at least 10 ppm CO and 10% of the samples contained at least 31 ppm CO.

b. Buses. Bulbuyan and Smulevich[3] analyzed the air inside 60 buses. The samples were taken over 2 hours. The mean levels during warm and cold season are as follows:

	mean mg/cu m (ppm)	
	warm season (ppm)	cold season (ppm)
carbon monoxide	42.3	56.5
hydrocarbons	177.2	216
nitrogen oxides	1.5	4.2
gasoline	166.8	114.4

The high pollution levels inside the buses during the cold season were due to engine emissions entering poorly-ventilated buses with windows usually kept shut.

Johnson et al.[4] examined the carbon monoxide levels in school buses in the Seattle area, following an incident in which eight children became ill from carbon monoxide in a school bus. The buses were examined after an estimated driving time of one to two hours, and after idling for two hours at a parking lot.

Concentration CO inside bus	% of total buses after driving 1-2 hrs.	after idling 2 hrs
0	52%	31%
trace to 8 ppm	36%	32%
9-34 ppm	9%	26%
35-49 ppm	3%	5%
50-100 ppm	--	--

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From the above results, several buses exceed 35 ppm of carbon monoxide, whether in running or idling conditions.

2. Carboxyhemoglobin Blood Levels of Motor-vehicle Drivers.

As early as 1958, Moureu compared the blood levels of various population groups in France, warning that the blood of drivers of motor vehicles contain, on the average, more carbon monoxide than that of workers exposed to stationary sources of carbon monoxide and to urban residents. The results for 1963 are as follows:[5]

Exposure groups	% Who Have COHb Levels > 4.8%
motor vehicle drivers	41%
workers exposed to CO	14%
urban residents	11%

The high level of carbon monoxide emitted from vehicles in Paris, reflected by elevated carboxyhemoglobin percentages has also been reported by Chovin in 1967.[6] The median for drivers was 5.0% carboxyhemoglobin, whereas the median for policemen was 2.0%. Boudene et al., in 1974, compared the carbon monoxide content of Parisian taxi drivers with a control group of residents.[7] The carbon monoxide content in the blood of drivers was higher than the controls. The comparison included the smoking habits of the drivers but there were no corresponding smokers among the controls so that it was not possible to contrast cigarette smoking alone with exposure to vehicular emission.

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An elevation of carboxyhemoglobin levels has been reported among London taxi drivers,[8] Belgrade drivers[9] and Amsterdam drivers.[10] In all these reports, there is a definite elevation of carboxyhemoglobin in motor vehicular drivers compared to non-drivers residing in the same city. Only the comparison of London taxi drivers by Jones et al.[8] has separated smokers from nonsmokers with the following results:

London taxi drivers (No.)	Mean ± S. D.	(Range)
smokers (29)	5.31 ± 2.6	(1.0-4.7)
nonsmokers (20)	1.55 ± 0.8	(0.4-3.0)

As in other comparisons, (Chapter 2), there is overlapping in blood levels between the two groups, and the standard deviation for smokers is larger than that for nonsmokers.

3. Cigarette Smoke Inside Vehicles.

There have been reports of levels of cigarette smoke inside vehicles, believed to be high enough to be of a health hazard to the occupants. The studies have been performed on nonventilated vehicles, a feature that is usually ignored when results are cited by others.

a. Passenger cars. In 1967, Srch[11] placed four subjects in a car with windows and doors closed. The engine was started with the car in the garage. The two smokers consumed 10 cigarettes in 62 min

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and analysis of the blood samples revealed the following:

	Mean % COHb		
	before	after	Δ
2 smokers	5	10	5
2 nonsmokers	2	5	3

The increase in carboxyhemoglobin levels in nonsmokers is brought about by carbon monoxide generated from the engine.

It is claimed by Srch[11] that cigarette smoke was the primary source of carbon monoxide but he did not separate vehicular emission from cigarette smoke.

Petrilli et al., reported carboxyhemoglobin levels inside cars with no smokers and with smokers.[11a] Only the minimum values for nonsmokers and the maximum values for smokers were reported, but the exact range for the groups were not mentioned. In any event, the reported minimum for nonsmoker and maximum for smokers were elevated as the carbon monoxide concentration in the car was raised from 50-90, to 60-120 ppm.

The most complete study of the effects of cigarette smoke on carbon monoxide level in a passenger car was performed by Harke and his collaborators[12, 13] in 1975. In an automobile stationed inside a wind tunnel, there were 4 passengers with the driver as a smoker. The windows and doors were closed, but the air jets and air blower were controlled. The carbon monoxide levels at various wind velocity, ventilation and cigarettes

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consumed were as follows:[12]

8-10 ppm = 2 x 3 cigarettes, air vents fully open, wind 0 km/hr.

10 ppm = 2 x 3 cigarettes, air vents fully open, wind 50 km/hr.

20 ppm = 2 x 3 cigarettes, air vents 1/2 open, wind 50 km/hr.

30 ppm = 3 x 3 cigarettes, air vents closed, wind 50 km/hr.

The above results indicate the importance of air exchange in determing the level of carbon monoxide from cigarette smoke inside a car. In the absence of ventilation, there is a rise of carbon monoxide concentration, a condition that is rarely reproduced in a real life situation.

The next group of measurements were carried out in automobiles driven through Hamburg. Under the condition of 2 x 2 cigarettes, doors and windows closed, the carbon monoxide levels inside the driven car were as follows:[13]

21 ppm = air vents closed, speed constant

15 ppm = air vents half open, speed constant

12 ppm = air vents open, speed constant

12 ppm = speed 80 km/hr, vents closed

24 ppm = speed 35 km/hr, vents closed

The importance of speed of the car and degree of ventilation is seen in the above results. Air ventilation and car movement reduce the concentration of carbon monoxide.

Normally, comfort dictates a degree of ventilation which minimizes carbon monoxide levels from cigarette smoking. One must also be conscious of the variation in the quality of ventilation systems between the more luxurious American-manufactured cars and many of the foreign compacts.

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b. Buses. Seiff conducted a study for the Federal Highway Administration to determine the levels of carbon monoxide inside a Greyhound bus that was stationary.[14] Cigarettes were burning to simulate two conditions: "worst case" condition with all passengers smoking, each one smoking half of the time; the "real world" condition in which the rear fifteen of the seating space occupied by smokers, each one smoking half of the time. In the "worst case" situation, the level of carbon monoxide was 33 ppm, with an ambient air level of 7 ppm, a difference of 26 ppm. The contribution of carbon monoxide from vehicular engine, was not measured separately from the cigarette smoke. In the "real world" situation, the level inside the bus was 18 ppm, ambient of 13 ppm and a difference of 5 ppm. It was the opinion of Seiff that these levels of carbon monoxide were below the standards set by the Occupational Safety and Health Administration.

c. Trains. Harmsen and Effenberger[15] monitored the quality of air inside train cars that were running in Hamburg in 1953. All windows and air vents were closed. Although smoking was permitted there was no increase of carbon monoxide level after 30 to 60 min of use. In one car, with 10 smokers, there was a rise of nicotine content to 2.5 mg/1000 liters, after 45 min. The significance of nicotine level is discussed in Chapter 9.

d. Ferryboat. Godin et al.[16] compared the carbon monoxide concentra-

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tions of compartments of a crowded Ward's Island ferryboat:

	CO ppm mean ± S. D. of 11 determinations
smoking compartment	18.4 ± 8.7
nonsmoking compartment	3.0 ± 2.4
difference	15.4 ± 8.2

The levels in the smoking compartment are still below the standard for occupational exposure.

e. Airplanes. The Federal Aviation Administration sampled the air during 20 international flights and 8 domestic flights of the Military Aircraft Command. In all samples, the carbon monoxide level did not exceed 5 ppm.[17]

4. Practical Aspects of Intravehicular Exposures.

The possibility that carbon monoxide contained in cigarette smoke would influence the nonsmoker passenger of a vehicle can be dismissed because the levels even in nonventilated vehicles are below the occupational standards for carbon monoxide. The question as to the influence of smoking on the driver can be answered by citing the investigation of Boek on automobile accidents.[18] There was no difference in accident involvement between smokers and nonsmokers noted by Boek, although a survey of workers by Fiandaca and Vercellotti[19] revealed a correlation between accident rate and exposure to

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carbon monoxide in the work environment. Motor vehicular accidents in the city of Los Angeles is not correlated with atmospheric carbon monoxide concentration, but there is an association of the number of accidents to the levels of oxidants in the ambient air.[20] The relationship may be a spurious one reflecting an increase in accidents resulting from heavier traffic, rather than the high level of pollutants causing more accidents. The fatalities from carbon monoxide poisoning inside vehicles[21] are extreme examples which do not relate to normal use of vehicles that are properly ventilated.

B. Extravehicular Exposure in Semienclosed Space

Workers of garages and tunnels are exposed to vehicular emissions that are not readily eliminated. The studies on smokers indicate that the amount of carbon monoxide from smoking is small compared to that emitted from vehicles.

1. Garage Operators.

The first examination of garage operators was reported by Hofreuter et al. in 1962.[22] In a group of vehicular inspectors in Cincinnati, they reported the following values for carboxyhemoglobin % saturation:

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	Mean ± S.D. (Range)
garage workers (68):	3.74 ± 1.89 (1.0 - 12.0)
smokers (54)	3.8
nonsmokers (14)	3.4

From the above, Hofreuter et al. concluded that the use of cigarettes was not reflected in a sustained difference between smokers and nonsmokers.

Other investigators have noted a difference between smokers and nonsmokers among garage and service station operators.[23-26] The results of Buchwald[23] from operators in Canada are as follows:

Amount smoked daily (no. of persons)	COHb % saturation Mean (Range) Median
nil (122)	5.0 (0 - 16) 4
1 - 9 (21)	6.4 (1 - 15) 4
10 - 20 (138)	8.5 (0.5-19) 8
>20	9.2 (1 - 18) 9

There is overlapping in the range of values for nonsmokers and smokers, although the means and medians are progressively higher with the amount of cigarettes smoked.

The most significant observations relate to the examination of garage employees, before and after a work shift.[27-30] Ramsey[27,28] reported the

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following changes in carboxyhemoglobin levels in a group of 38 parking garage workers:

Time blood collected	Mean ± S.D. (Range)
8:00 A.M.	2.4 ± 1.74 (0.4 - 6.9)
5:00 P.M.	8.4 ± 3.33 (2.9 - 15.8)

The exposure of the workers was estimated to be 59 ppm of carbon monoxide in the work environment. Out of the 38 employees, the breakdown of smokers and nonsmokers were as follows:[27]

Time of collection	Mean ± S.D. for COHb %	
	24 Smokers	14 Nonsmokers
8:00 A.M.	2.9 ± 1.88	1.5 ± 0.83
5:00 P.M.	9.3 ± 3.16	7.3 ± 3.46
difference	6.4	5.8

The most significant feature of the above results is that the uptake of carbon monoxide during a working day (about 6%) is four times higher than the difference between smokers and nonsmokers (1.5%). The amount of carbon monoxide absorbed from smoking is small compared to the amount from exposure to vehicular emission in a garage. Ramsey[28] has further described a reduction in reaction times in drivers exposed to carbon monoxide levels seen in garage operators.

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2. Longshoremen.

In the course of operating fork lift trucks in ship holds or unloading of cars, longshoremen are exposed to carbon monoxide emitted from vehicular motors.[31-34] Smokers absorb less carbon monoxide from the ship holds than nonsmokers.[1] Gibbs et al.[31]

blood samples collected:	Median (Range) for COHb % 39 smokers	12 nonsmokers
arrival at work	3.4 (0.5 - 11.2)	0.6 (0 - 1.6)
end of first period	3.4 (0.0 - 8.3)	2.0 (0 - 5.0)
difference	0	1.4

The phenomenon of no uptake of carbon monoxide seen in smokers is explained by their level of carboxyhemoglobin upon their arrival. The level of 3.4% is enough to reduce the absorption of carbon monoxide from their work environment (see Chapter 1).

3. Tunnel Traffic Officers.

The concentration of carbon monoxide in tunnels vary according to the density of vehicular traffic and velocity of air flow.[35] Although the levels can reach as high as 250 ppm, the concentration is usually below 100 ppm.[36]

An examination of a group of 156 Holland Tunnel traffic officers exposed throughout a period of 13 years to an occupational level averaging 70 ppm did not reveal any evidence of injury to health attributable to carbon monoxide.[37]

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In a more recent health examination of the employees of the New York City Tunnel authority exposed to an average level of 63 ppm, the carboxyhemoglobin levels were as follows: 2.93 ± 1.36% for nonsmokers and 5.01 ± 2.25% for smokers.[38] As in other comparative groups, the standard deviation for smokers is larger than in nonsmokers (Chapter 2). There was no influence of smoking in ventilatory function. Although the closing volume was higher in both smokers and nonsmokers compared to hospital maintenance workers, carbon monoxide exposure cannot explain the difference because the air inside the tunnel also contained significant amounts of lead, nickel, hydrocarbons, nitrogen oxides, aldehydes and acrolein.[38]

C. Inhalational Toxicity of Vehicular Exhaust Gas

Since carboxyhemoglobin levels of passengers and vehicular drivers are determined by the amount of carbon monoxide emitted by the engine, it is important to review the effects of total vehicular exhaust gas. In 1921, Hendersen et al. reported the physiological effects of automobile exhaust gas on human volunteers in a chamber.[39] The standards of ventilation for brief exposure to carbon monoxide were based on the concentrations that did not elicit dizziness, headache and nausea, the first perceptible signs of carbon monoxide intoxication. Repeated daily exposures to 200, 300 and 400 ppm, 4 to 7 hours daily for 68 days were performed on a group of human volunteers by Sayers et al. in 1929.[40] Four hours of exposure

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to 200 ppm caused frontal headache to appear in some subjects, with a level of 20% carboxyhemoglobin saturation. Following the report of Henderson et al. there were studies of toxicity of exhaust gases and carbon monoxide in air mixtures. The limited number of investigations using exhaust gas per se are discussed in the remainder of this chapter.

1. Humans.

Holland et al.[41] exposed students in a chamber containing exhaust gas with 15 to 29 ppm of carbon monoxide. After a few hours of exposure, there was no alteration in the performance of fine neuromuscular tasks, e.g. reaction time or cardiorespiratory work efficiency. There have been no other reported studies on humans exposed in chamber containing exhaust gas.

2. Dogs.

Vaughan et al. exposed 104 beagles for 18 months to natural and photochemically reacted auto exhaust gas.[42] The concentration of carbon monoxide was 100 ppm, with 24 to 30 ppm of hydrocarbons, 0.1 ppm of nitrogen dioxide and 1.5 - 2.0 ppm of nitrogen oxide. There were no differences in diffusing capacity, pulmonary compliance, and pulmonary resistance between exposed and control dogs. The other investigations used individual constituents of exhaust gas rather than the total mixture[43,44] so that there is no information on the threshold concentration of exhaust gas that would influence the canine lungs when administered for prolonged periods.

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3. Rabbits.

The exhaust gas used on rabbits contained as much as 1,000 ppm CO which caused a temporary increase in dust elimination capacity of the trachea and later a decrease.[45] In the other exposure studies, lower concentrations of exhaust gas (30 ppm CO) were used but there were no measurements of lung function.[46,47]

4. Guinea Pigs.

The most widely used species for inhalational toxicity is the guinea pig. Swan and Balchum[48] maintained animals for prolonged periods and noted an increase in airway resistance when the ambient air exceeded the following levels: 40 ppm carbon monoxide, 16 ppm hydrocarbons, 1.2 ppm nitrogen oxides and 0.2 ppm oxidants. In anesthetized guinea pigs, each of the pollutants has been demonstrated to depress the myocardium and constrict or dilate the airways.[50,51]

5. Rats and Mice.

The experiments on rats and mice indicate that chronic exposure to exhaust gas produce alveolar lesions,[52-54] pulmonary tumors[55-58] and bronchial inflammation.[59] The threshold concentrations reported for the various constituents have been variable indicating differences in susceptibility of strains and in exposure schedule.[60,61] The results so far indicate that the components of exhaust gas, when inhaled produce lung lesions which cannot be duplicated by administration of carbon monoxide.

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D. Practical Aspects of Vehicular Exposure.

Although results of animal experiments indicate that vehicular emissions when inhaled produce pulmonary lesions, it has not been possible to ascertain the human threshold levels in man. The level of carboxyhemoglobin in the blood has been used as the tracer for the amount of human exposure to vehicular emission as well as to cigarette smoke. The interpretation of epidemiologic data has been difficult because the effects from cigarette smoking are distorted by the exclusion of those arising from vehicular emission. Studies that recognize the dual source of carbon monoxide have evaluated the influence of cigarette smoking as less important than the exposure to vehicular traffic.

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Chapter 8

SMOKERS AND NONSMOKERS OUTDOORS

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The level of air pollution is an important consideration in evaluating the significance of carboxyhemoglobin in the blood of smokers and nonsmokers. The carbon monoxide in the ambient air from moving or vehicular sources, as well as from stationary or occupational emission, is absorbed in the blood as readily as that contained in cigarette smoke. The amount detected in blood as carboxyhemoglobin represents the sum of all the exogenous sources plus the amount produced endogenously in the body.

It has been suggested that low levels of carboxyhemoglobin (about 5 to 10% saturation) are fatal to patients with heart or bronchopulmonary disease. The suspicion is based on the interference by carboxyhemoglobin with the oxygen-carrying capacity of the blood. It is further postulated that the diseased heart would suffer from lack of oxygen and that the lungs will not deliver sufficient amounts of oxygen to the alveolar capillaries for absorption by the blood with elevated carboxyhemoglobin. The result is myocardial infarction and death in the cardiac patient, and dyspnea and respiratory failure in the patient with bronchopulmonary disease.

The above hypothesis on the dangers of low level of carboxyhemoglobin is based on interpolation of results of several epidemiologic and experimental observations that are reviewed in this chapter. The problem is largely of interpretation of data and their relevance to both the cigarette smoker and the nonsmoker with preexisting cardiopulmonary disease. The question of smoking per se in the causation of disease has been discussed in Chapters 2, 3, and 4.

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A. Patients with Cardiac Disease

In the June, 1976 issue of Annal of Internal Medicine, Green, Cohen and Kurland[1] reported a 44-year old male who collapsed on the streets of Boston on a day when ambient temperature was 26°C and humidity was high.

If the man lived a sedentary style and was a heavy smoker, he would be considered as one example of sudden deaths from acute myocardial infarction with arteriosclerotic coronaries, that have been reported repeatedly in the literature during the past 20 years. The amount of air pollution, together with carboxy-hemoglobin from smoking would be said to have triggered the fatal event.

But the patient was a marathon runner who was a nonsmoker; death was from myocardial infarction but the coronaries were "widely patent" and there was no evidence of old or recurrent occlusion.

Green et al.[1] reported the case to be the first documentation of a myocardial infarction in a trained athlete while participating in a marathon.

Advocates of long distance running for prevention of or rehabilitation from ischemic heart disease should be not only aware of this possible complication, but also should question the supposition that episodic maximal exertion bestows a beneficial effect on the coronary arteries. How adequate is the exercise performance test for evaluating a beneficial effect on the coronary arteries? Since the exercise test has wrongly led to misconceptions on the value of marathon running, can the test continue to be accepted in the evaluation of the effects of air pollutants?

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1. Exercise Performance Test.

The results of Aronow et al. on anginal patients on a treadmill have been reviewed in Chapter 2. The reduction in exercise time until the onset of angina was reduced in patients who have been exposed to freeway atmosphere or to inhalation of low level carbon monoxide. Although the treadmill showed a reduction in performance in subjects inhaling carbon monoxide,[2-9] actual athletic performances in competitive meets of cross-country track runners is not effected by carbon monoxide concentration but is correlated with the oxidant level in the ambient air.[10]

2. Mortality Statistics.

In an analysis of 1,075 coroners' cases in Los Angeles, Curphrey et al.[11] found no correlation between the incidence of myocardial infarction with carboxyhemoglobin levels, for both nonsmokers as well as smokers. Goldsmith et al.[12,13] arrived at an opposite conclusion, i.e. fatality rate among 3,080 patients with myocardial infarction admitted to 34 Los Angeles hospitals is greater in high pollution areas than in low pollution areas. The difference in conclusion is based on the source, i.e. hospital records against coroners' cases. It is pertinent to point out that a similar study conducted in Baltimore failed to find a correlation between carboxyhemoglobin level and incidence of heart attacks. (Chapter 3). Consideration of other related information indicates that the incidence of myocardial infarction is not correlated with the level of carbon monoxide exposure.

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B. Patients with Bronchopulmonary Disease.

Although the incidence of respiratory symptoms relates to the level of carboxyhemoglobin in the blood,[14] the coincidental exposure to air pollutants is the determining factor.[15, 16] This suspicion is based on the experimental work showing that carbon monoxide does not induce dyspnea or produce lung lesions, whereas pollutants such as sulfur dioxide, nitrogen oxides and hydrocarbons do (Chapter 7). Reichel et al.[17] exposed 44 persons to street traffic for three hours and found no respiratory restrictions indicating that the effect is seen after prolonged exposure to pollutants.

The correlation of levels of air pollution with incidence of respiratory disease was detected by Sterling et al.[18, 19] in an analysis of morbidity as indicated by the length of stay in Los Angeles hospitals of patients. Smoking habits were not included in the analysis so that it is not possible to verify the earlier conclusion of Goldsmith and Deane[20, 21] that respiratory symptoms were found to occur more frequently among cigarette smokers than nonsmokers of outside workman in the Los Angeles area.

C. Carboxyhemoglobin Levels Following Exposure to Atmospheric Pollution

1. Blood Samples Before and After Work.

The uptake of carbon monoxide from the ambient air has been demonstrated

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by analysis of blood samples from traffic policemen, pedestrians and commuters. A rise in carboxyhemoglobin values reflects the amount of carbon monoxide absorbed. In some studies, a distinction is made between smokers and nonsmokers.[22-24] The results obtained by De Bruin et al. from a group of policemen in Amsterdam are as follows:

Subjects (no.)	Before Work Mean ± S.D.	After Work Mean ± S.D.	Δ Mean
smokers (14)	4.62 ± 0.97	5.16 ± 0.81	+0.54
nonsmokers (10)	1.43 ± 0.26	1.66 ± 0.27	+0.23

The uptake of carbon monoxide is small and is an indication of the level of pollution in the city of Amsterdam. In the center of Cairo, Emara et al.[25] reported the following mean values:

Subjects	Before (mean)	After (mean)	Δ (mean)
smokers	1.9	9.5	7.6
nonsmokers	0.9	4.5	3.6

There is no mention of range of values and the number of subjects so that it is impossible to interpret the increased uptake of smokers compared to nonsmokers.

Morando and Rovida[26] reported opposite effects in traffic policemen during the course of their work at Via Milano, Genova.

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Subjects	Before (mean)	After (mean)	Δ (mean)
smokers	3.40	3.00	-0.40
nonsmokers	1.83	2.20	+0.37

The reduction in carboxyhemoglobin levels among smokers is in contrast to the increase in nonsmokers. The results are different from those reported from Cairo and Amsterdam.

2. Single Blood Samples.

The remaining studies of carboxyhemoglobin levels consist of single blood samples per individual, taken before, during or after exposure to the polluted air. The differences between smokers and nonsmokers are as follows:

Subjects	Smokers % COHb Mean ± S.D. (Range)	Nonsmokers % COHb Mean ± S.D. (Range)
New York City		
Bridge operators[27]	5.01 ± 2.25	2.93 ± 1.36
Pedestrians[27]	3.84 ± 2.06	1.94 ± 0.62
Stockholm		
Policemen[28]	3.5 ± 1.17 (1.5-6.2)	1.2 ± 1.17 (0.5-2.0)
Malmo		
Policemen[28]	5.0 ±2.44 (3.2-9.7)	0.8 ± 0.14 (0.7-1.1)
Erlangen - Nurnberg		
Dustmen[29]	5.1 ± 2.7	1.4 ± 0.64

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	Smokers % COHb	Nonsmokers % COHb
Athens		
Pedestrians[30]	(2-4)	(0.5-1.0)
Bordeaux		
Policemen[31]	2.35	1.23
Milan		
Pedestrians[32]	2.65 ± 0.99	1.60 ± 0.64

The last study tabulated above is by Grisler et al.[32] who reported differences in subjects living in the center of the city compound from those observed among rural inhabitants.

The above results indicate considerable overlapping in values for smokers and nonsmokers. The same phenomenon has been discussed in earlier chapters.

D. Practical Aspects of Carbon Monoxide in the Ambient Air

Smokers and nonsmokers respond differently in the amount of carbon monoxide they absorbed from the ambient air. The difference is not fully appreciated because the results of various studies show that the uptake of carbon monoxide is either higher or lower in smokers than in nonsmokers. The explanations for the variability are discussed in Chapter 1 and largely depend on the preexisting level of carboxyhemoglobin for both groups.

The information reviewed in this chapter has been used by organizations as bases for recommended air quality standards.[33-36] The amount of carbon

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monoxide from the ambient air outdoors is usually overlooked in the consideration of carboxyhemoglobin levels of smokers and nonsmokers.

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Chapter 9

NONSMOKERS AND SMOKERS INDOORS

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The recent claim that cigarette smoke is a health hazard to the nonsmoker is based on interpolation of several experimental observations that include elevation of carbon monoxide (greater than 25 ppm) in smoked-filled enclosures such as a sealed chamber or a nonventilated conference room. Actual measurements of carbon monoxide in residential houses, offices and public places show that levels rarely exceed 10 ppm, a concentration that is no different from outdoors.

The epidemiologic studies on children show a relationship of parental smoking to incidence of respiratory symptoms and this correlation has been interpreted as the consequence of exposing children to cigarette smoke. There are other variables in these comparisons which can explain the correlation of parental smoking with respiratory symptoms, such as inherited susceptibility to disease, socioeconomic factors, contagion of infectious diseases, and levels of indoor pollution.

This chapter reviews the literature relating to the effect of cigarette smoke on the nonsmoker. The information is presented according to its source separating measurements made in living quarters and public places from those made in artificial situations created in the laboratory.

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A. CONCENTRATION OF CIGARETTE SMOKE INDOORS

The concentration of cigarette smoke indoors is usually estimated by the analysis of carbon monoxide, based on the assumption that its major sources which may become more important than cigarette smoke, such as burners and stoves indoors and vehicular traffic outdoors. The other constituents of cigarette smoke, such as nicotine, acrolein and benzypyrene, have also been used as tracers for cigarette smoke but the techniques are more complex than the methods for analyzing carbon monoxide.

1. Home Environment.

There is no published measurement of carbon monoxide from cigarette smoke in residential houses. To the contrary there are several reports indicating that the carbon monoxide indoors originates from vehicular emissions outdoors, burners for house heating and kitchen stoves.

a. Vehicular traffic outdoors. The carboxyhemoglobin levels of individuals residing in areas of heavy vehicular traffic are higher than those with light traffic. The mean values for residents in Tokyo are as follows:

City	COHb % mean	
	heavy traffic	light traffic
Tokyo	4.27	2.79

The smoking habits of the residents examined by Suzuki et al.[1] in the above results were not known. Oyagi et al.[2] arrived at the same conclusion based on

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measurements of carbon monoxide in the expired air. They included that families residing close to traffic absorbed not only carbon monoxide but other motor exhaust gases such as lead and benzypyrene.

Derouane[3,4] compared outdoor and indoor levels of carbon monoxide in private homes in Liege. In the absence of indoor sources of carbon monoxide, the indoor concentration is 66 to 87% of the outdoor level of carbon monoxide.

b. Heating burners. The carboxyhemoglobin levels of residents in Tokyo were compared during the cold months requiring house heating and the months that did not. The results of Watanabe et al.[5] are as follows:

City	COHb Range	
	summer	winter
Tokyo	0.7-2.3	1.5-4.5

The above levels indicate that the use of heaters contributes a significant amount of carboxyhemoglobin. Biersteker and DeGraaf[6] examined homes in Rotterdam during the winter months and reported that the levels of carbon monoxide are

In the United States, Yates[7] examined 1,061 combustion appliances in 372 residential establishments. Forty percent of the homes investigated contained one or more appliances that were found to be emitting carbon monoxide. About 25% of all appliances listed were discharging carbon monoxide into the room atmosphere and 24% of those that were found positive were emitting carbon monoxide in the range of 200 ppm and over. In the house that contained the positive-emitting appliances, 40% of the residents gave clinical histories of mild carbon monoxide exposure.

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c. Kitchen burners. The major sources of carbon monoxide in the kitchen are gas burners[8] and frying pan.[9] Wade et al. sampled the air in four private houses which had gas stoves. The indoor level of carbon monoxide reached as high as three times the outdoor level.

d. Other pollutants indoors. The survey of houses by Wade et al.[10] also revealed that nitrogen oxide and nitrogen dioxide from the concentration of particulates is increased in the daytime and reduced at night when there was no household activity.[11, 12] It is necessary to realize that pollutants other than carbon monoxide are present in the home environment when the suspected diseases associated with cigarette smoke exposure are discussed.

2. Public Places.

The concentrations of carbon monoxide and benzypyrene in public places are influenced by outdoor and indoor sources. The only tracer that is specific for cigarette smoke is nicotine. Carbon monoxide although widely used to estimate levels of cigarette smoke indoors, is not appropriate for this purpose because there are indoor and outdoor sources of carbon monoxide.

a. Office buildings. In an office building in Oslo, von Ubisch and Westerlund[13] continuously monitored the carbon monoxide levels inside a conference room. Although the concentration of carbon monoxide started at 2 ppm in the morning, it rose to 12 ppm in the evening. This increase was not caused by smoking but reflected the denser traffic in the ares which was seen in the concentration of carbon monoxide in the air intake into the building. Godin et al.[14] observed the same phenomenon in an office building in Toronto. The indoor carbon monoxide

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concentration mirrored the outdoor level, with a lag of one to two hours. Kimura[15] reported the concentration of offices in Japan ranging from 2 to 11 ppm. In an office building in London, Cole[16] reported the levels of carbon monoxide ranging from 3 to 8 ppm. Harke[17] carried out continous measurements in office buildings located in Hamburg. The mean level in one air conditioned building and in another non-airconditioned building never exceeded 5 ppm. In a room of 78.3 cubic meters occupied by 3 smokers, the 30-min value of 9 ppm was measured and reached a peak of 15.6 ppm.

b. Restaurants and bars. The following levels of carbon monoxide have been reported in the following places:

Vancouver, large cafeteria	[18]	less than 10 ppm
Cincinnati, two taverns	[19]	mean 12.5 ppm

Benzypyrene has also been detected in a large cafeteria and beer parlor in Vancouver,[18] as well as in a restaurant in Prague.[20] However, the kitchen as a primary source of benzypyrene could not be excluded.

c. Theaters, arenas, and stations. The levels reported at public places are as follows:

		CO ppm
Toronto: theatre auditorium (smoking prohibited)	[14]	1.4 ± 0.8
theatre foyer (smoking permitted)		3.4 ± 0.8

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	CO ppm
Vancouver: theatre lobby[18]	less than 10 ppm
political convention	less than 10 ppm
bingo game in large hall	less than 10 ppm

In addition to carbon monoxide, nicotine has been detected in the atmosphere of public places in Hamburg[21] and Boston.[22] The following concentrations were reported by Hinds and First:[22]

Boston (no. of samples)	Nicotine µg/meter^3 (mean)
Bus waiting station (2)	1.0
Airline waiting station (2)	3.1
Cocktail lounge (3)	10.3
Student lounge (1)	2.8
Restaurant (4)	5.2

Hinds and First[22] calculated the equivalent amount of filter cigarettes per hour that would generate the levels of nicotine tabulated above. They concluded that the nonsmoker was inhaling the equivalent of less than one-hundredth of a cigarette per hour.

B. EXPERIMENTAL OBSERVATIONS IN NONVENTILATED ROOMS

The most widely quoted levels of carbon monoxide in smoke-filled rooms were taken from nonventilated or poorly ventilated rooms. The results are as follows:

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	no. of cigarettes/ 10 cu m/hour	CO concentration ppm
Harmsen and Effenberger, 1957[21]	6	80
Lawther and Commins, 1970[23]	5	20
Harke et al., 1972[24-28]	3	8
Anderson and Dalhamm, 1973[29]	4	4.5
Russell et al., 1973[30]	20	38

There is no correlation of the number of cigarettes to carbon monoxide concentration because of the variability in ventilation from study to study. The most extreme situation which had a concentration of 80 ppm was in a non-ventilated room. Harke et al.[24-28] compared various rooms at different levels of cigarette consumption. In the same room with fixed numbers of cigarettes, ventilation reduced the level of carbon monoxide from 8 ppm to less than 5 ppm.

1. Carboxyhemoglobin Levels.

Some of the experimental observations listed above included measurements of carboxyhemoglobin levels in nonsmokers before and after exposure in a smoke-filled room.

	CO level	COHb mean ±S. D.(Range) Before	After
Harke, 1970[24]	30	0.9±0.1(0.7-1.1)	2.1±0.1(2.0-2.3)
	5	0.9±0.1(0.7-1.0)	1.3±0.1(1.2-1.6)
Russell et al., 1973[30]	38	1.6±0.6(0.7-2.2)	2.6±0.7(1.7-4.2)

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The above results indicate a rise of about 1% COHb at a room concentration of 30 to 38 ppm. In addition, Anderson and Dalhamn[29] reported no change at a carbon monoxide concentration of 5 ppm.

The major shortcoming of the measurements of carboxyhemoglobin levels in subjects and the carbon monoxide concentration in rooms that are poorly ventilated is that there are no control observations to determine diurnal variations in a room without generation of cigarette smoke. It is necessary to subtract the outdoor levels of carbon monoxide from the indoor levels to obtain the amount attributed to cigarette smoke.

2. Nicotine Absorbed.

Harke[24] estimated the amount of nicotine absorbed by the nonsmoker in smoke-filled room to be about 1% of that absorbed by the smoker. In another smoke-filled room, Horning et al. reported the nicotine absorbed by the nonsmoker to be 5% of that absorbed by smokers.[31] The difference between 1% and 5% absorption of nicotine is probably based on the technique for estimation of nicotine absorbed. The 1% amount absorbed by the nonsmoker is close to the less than 1% estimated by Hinds and First based on analysis of air (see A above).

3. Acrolein and Acetaldehyde.

While the amounts of acrolein and acetaldehyde in the ambient air have been analyzed the amounts absorbed have not yet been determined. Harke et al.[27] used

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an unventilated room of 38.2 cubic meters filled with smoke generated from cigarettes by a smoking machine; 30 cigarettes were burned within 13 min. The amounts of acrolein and acetaldehyde measured 11 to 23 min later were: 0.45 mg acrolein/ cu m and 6.5 mg acetaldehyde/ cu m. When 5 cigarettes were burned within 13 min, the respective concentrations were 0.07 mg acrolein/ cu m and 1.3 mg acetaldehyde/ cu m. In additional observations using a larger room (170 cu m), the concentrations of acrolein, acetaldehyde and carbon monoxide were as follows:

	acrolein (mg/ cu m)	acetaldehyde (mg/ cu m)	CO ppm
150 cig. in 30 min	0.38	4.2	53
102 cig. in 30 min	0.21	1.9	28
108 cig. in 2 hr.	0.15	1.7	24.5

From the above results, it would appear that there is a direct relationship between the concentrations of acrolein, acetaldehyde and carbon monoxide.

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C. EXPERIMENTAL OBSERVATIONS IN CHAMBER FACILITIES

Since the amount of carbon monoxide generated from a burning cigarette can be measured, it has been possible to derive equations on the expected concentration based on the number of cigarettes, size of the chamber and air ventilation.[32-37] The equations have been verified by actual analysis of carbon monoxide in a chamber under controlled conditions.[38,39] and have been used to calculate the necessary ventilation to avoid accumulation of carbon monoxide.[40-44] It has become apparent that the suspended particulate matter from outdoor and indoor sources are not adequately reduced by air conditioning.[45,46] The information derived from chambers are more relevant to spacecraft and submarine than to the residential and public buildings.

D. EFFECTS OF CIGARETTE SMOKE ON THE HEALTH OF NONSMOKERS

The information on the health effects of cigarette smoke is derived in part from the simulated smoke-filled rooms described above (B and C) as well as from surveys and epidemiologic studies. The results have been contradictory

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for cardiovascular system, respiratory system and mental performance.

1. Cardiovascular System.

There are only two groups of observations relating to the cardiovascular effects of cigarette smoke on the nonsmoker. The first was made by Luquette et al.[47] who exposed 51 elementary school children in a poorly-ventilated enclosure containing cigarette smoke. An acceleration of heart rate and an increase in systolic and diastolic blood pressure were noted in the course of watching a film. It has not been possible to ascertain if the cardiovascular reaction is caused by the film or the cigarette smoke or both. Harke et al.[26] observed 30 adults in a nonventilated room full of cigarette smoke and found no alterations in the electrocardiogram, blood pressure or pulse frequency in response to the cigarette smoker. That the two groups of researchers reached distinctly opposite conclusions may be explained by differences in the following factors: (a) Age--children are more likely to react to a social environment than adults who repress their reactions. (b) carbon monoxide concentration in the room--measured by Harke et al.[26] but not by Luquette et al.[47] (c) Ventilation of the room--absent in one study and poor in the other.

2. Incidence of Respiratory Disease in Children.

Cameron[48] has surveyed by telephone 1,000 residences in Denver. The respiratory disease rate for children when members of the family smoked, was between 31 and 33%, as compared to 20 to 29% for children without a smoker in the family. However, the same study failed to find a correlation between smoking and the incidence of disease among adults. The author has explained the paradox as being due to greater anxiety of smokers which makes them more aware of

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disease in their children, to the influence of smoking, alcohol and coffee upon progeny in utero, which has weakened resistance for smokers' children; or to the fact that smokers themselves are used to their habit-linked maladies and, therefore, report only the more severe afflictions, unlike nonsmokers. In a subsequent survey of 727 households, Cameron et al.[49-51] found that smokers' children were sick more frequently than those of nonsmokers. While psychological reactions of the children were examined,[52] their allergic background was not explored, so that one cannot exclude this latter factor as a possible cause of the difference in prevalence of illness.

Norman-Taylor[53] examined the records of 5-year old new entrants to school and noted that the history of respiratory troubles grows as the level of domestic smoking increases. The author cautioned against too-hastily excluding such socioeconomic factors and cited as an example of the doubtless compounding of medical and extra-medical influences, the fact that low income families tend to smoke more than high income families.

Colley and his collaborators[54-57] have been surveying children of various age groups. Over the first five years of life, the incidence of pneumonia and bronchitis in the first year of life was associated with parents' smoking habits, i.e. lowest incidence was where both parents were nonsmokers and highest was where both smoked. The association was not consistent after the first year of life to the fifth year. From 6 to 14 years of age, there was a close association between parents' and children's respiratory symptoms independent of parents'

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smoking habits. The history of illness in childhood correlates with the incidence of chronic respiratory symptoms in adulthood. The investigators could not exclude a genetic susceptibility of the children to respiratory diseases inherited from their parents. Another factor is the level of pollution from burners indoors[58] and vehicular emissions outdoors,[59-61] both of which influence the incidence of respiratory disease in both parents and children. The association of parental smoking and incidence of children's disease can be explained by these coincidental factors affecting both parents and children.

3. Subjective Reactions of Nonsmokers.

There is a considerable confusion in the nature of the complaints of nonsmokers who object to the presence of cigarette smoke. The most extreme opinion is that it is a syndrome of "severe sensitivity to smoke . . . among the symptoms are loss of memory, light headedness, difficulty in concentration, depressive personality changes, double vision and short blackouts . . . coupled with headaches, eye irritation and nasal congestion."[62] The phenomenon appears to be a psychosocial reaction to the irritant action of tobacco smoke.

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a. Odor and irritation of mucosa. The odors of tobacco smoke derive from the presence of nicotine, pyridine, ammonia, aldehydes, volatile oils and other substances. There is a decrease in odor perception level with an increase in either humidity or temperature.[41] Yaglou[42] investigated nonsmoker complaints to the presence of unpleasant odors as well as to irritation of the eyes, nose or

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throat. The strength of tobacco smoke odor was evaluated by the sense of smell alone according to an arbitrary 5 point scale ranging from 0 (to mean imperceptible odor or irritation) and up to 5 (very strong odor or intolerable irritation). A room with 1,410 cubic feet of space was occupied by 3 non-smokers and 6 smokers; the latter consumed approximately 24 cigarettes per hour. There were also observers in an adjoining room who entered the test chamber to appraise the strength of odor and irritation. The test chamber was ventilated with air supplies of 6, 14, 26, 35 and 60 cfm (cu feet/min) per smoker. The ventilation required to remove objectionable cigarette smoke odors was as follows:

observers upon entering the room: no odor when 35 to 40 cfm/smoker per smoker

nonsmokers in the room: 25 cfm/smoker for odor; below 15 cfm for irritation

smokers in the room: unable to smell smoke odor; complained of irritation below 15 cfm/smoker.

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On the basis of the above results, Yaglou[42] suggested that ventilation requirements be based on the amount of tobacco consumed in a unit time, rather than on the total number of occupants. Ventilation at a rate less than 15 cfm/smoker caused irritation in both smokers and nonsmokers, whereas perception of odor by the nonsmoker was avoided when the supply of outside air was at least 25 cfm/smoker.

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A similar scale for evaluating odor and irritation was used by Halfpenny and Starrett[43] in studies of the ventilation requirements of air carriers. An odor chamber 7 ft long and 103 ft in diameter was constructed to provide space for 8 subjects. The concentration of cigarette smoke in the chamber was defined as the amount of tobacco burned (mg/min) divided by the air flow (cfm). Irritation of the eyes, nose and throat, which was just perceptible at a concentration of 0.6 mg/cu ft, became definite at 1.0 mg/cu ft and was judged objectionable at 3.0 mg/cu ft. Smoking surveys were conducted during 9 flights, sponsored by the Federal Aviation Administration.[63] The data showed a remarkably constant percentage of smokers among the passengers (54.8%). Collection of cigarette butts allowed calculation of the amount of tobacco smoked/smoker/hour, which amounted to 0.807 g with a standard deviation of 0.222. On the basis of statistical data concerning national smoking habits, the authors predicted that the most probable contamination rate aboard commercial aircraft is 0.412 g tobacco consumed/passenger/hour. Thus, the current aircraft practice of supplying 25 cfm/min of fresh air per person is adequate to control odor and irritation from cigarette smoke. Health aspects of smoking in transport aircraft have been reviewed by the Federal Aviation Administration.[63]

Johansson and Ronge[64] used an odor chamber with a space of 6.7 cu m. The ventilation required to avoid eye irritation in the nonsmoker was 12 cu m? hour/cigarette; to prevent nose irritation the requirement was 32; and to eliminate annoying odors in dry and warm air, it was 50.

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b. Tobacco Hypersensitivity Versus Irritation. There is some confusion in identifying the effects of cigarette smoke on nonsmokers, whether it is a form of allergy or a form of irritation, as described above. For the bronchial asthmatic, the earliest report of irritation to cigarette smoke was made by Hogner in 1920. He described a child suffering from bronchial asthma which he attributed to smoking by members of his family.[65] Brown has estimated that 1% of asthmatics are allergic to tobacco smoke (cited by Pipes).[66] In 400 households, the incidence of parental smoking was about the same in asthmatic children's homes as in those of controls.[67] Speer[68] collected data on 441 nonsmokers who developed symptoms when exposed to tobacco smoke and concluded that the effect of tobacco smoke appeared to be of irritative rather than of allergic character. This he based on the following findings: similar reactions occurred in allergic and nonallergic individuals and allergic manifestations like urticaria and eczema were absent.

The question of skin testing as a form of evaluating allergy to tobacco is beyond the scope of this review because carbon monoxide is not an allergen.

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c. Mental attitude. Rummel et al.[69] exposed 56 nonsmoking college students in a closed environment with cigarette smoke. Those who objected to being in the presence of cigarette smoke have significantly higher heart rates than those who did not object. In another study, Kidd[70] reported better scores in examinations for both smokers and nonsmokers when they were tested in separate rooms.

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than when the two groups took the same examination together in one room. The low scores were explained by the investigator as an emotional reaction of the nonsmoker and possible guilt feelings of the smoker from the disapproval expressed by nonsmokers.[70]

E. PRACTICAL ASPECTS OF NONSMOKER QUESTION

According to the information reviewed in this chapter, the presence of cigarette smoke in public places is not a health hazard to the nonsmoker for the following reasons: First: actual measurements in public places show low levels of carbon monoxide and nicotine. Second: There is no evidence that nonsmokers, when exposed to cigarette smoke, develop cardiovascular reaction or suffer respiratory distress. The subjective complaints of smokers are a combination of the psychosocial reaction with irritation of mucosa in extreme conditions of excessive amounts of cigarette smoke in poorly-ventilated enclosures. Several authorities have concluded that cigarette smoke in public places is not a health hazard to the nonsmoker.[71-75] The opposite conclusion by some authorities[76-86] is based on the observations of elevated levels of carbon monoxide seen in chambers or in nonventilated rooms, and a misinterpretation of data on tobacco allergy and respiratory diseases of children. At the present time, the question of the effect of cigarette smoke on the nonsmoker continues to be controversial. The answer will depend ultimately on the consideration of a more fundamental question, i.e. the difference between smokers and nonsmokers in general. These two groups are apparently distinguishable by factors other than the use of cigarettes.

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APPENDIX

The literature on carbon monoxide and cigarette smoking is covered in the bibliography of the preceding nine chapters. All the articles that contain original data are included in the bibliographies, totaling 862 references.

The articles that do not relate directly to cigarette smoking have been omitted from the nine chapters. They are in the appended list of supplemental bibliographies covering:

Page

Smoking and High Altitude: Opinions and Experiments on High Altitude. (50) 227

Pregnancy and the Reproductive System: Opinions and Experiments on the Reproductive System. (97) 232

Nonsmoker Question: Opinions on Passive or Involuntary Smoking. (93) 241

The above list of supplementary bibliography (total 240 titles) and the bibliographies of nine chapters (862 references) were derived from an original collection of 3700 articles on the broad subject of carbon monoxide.

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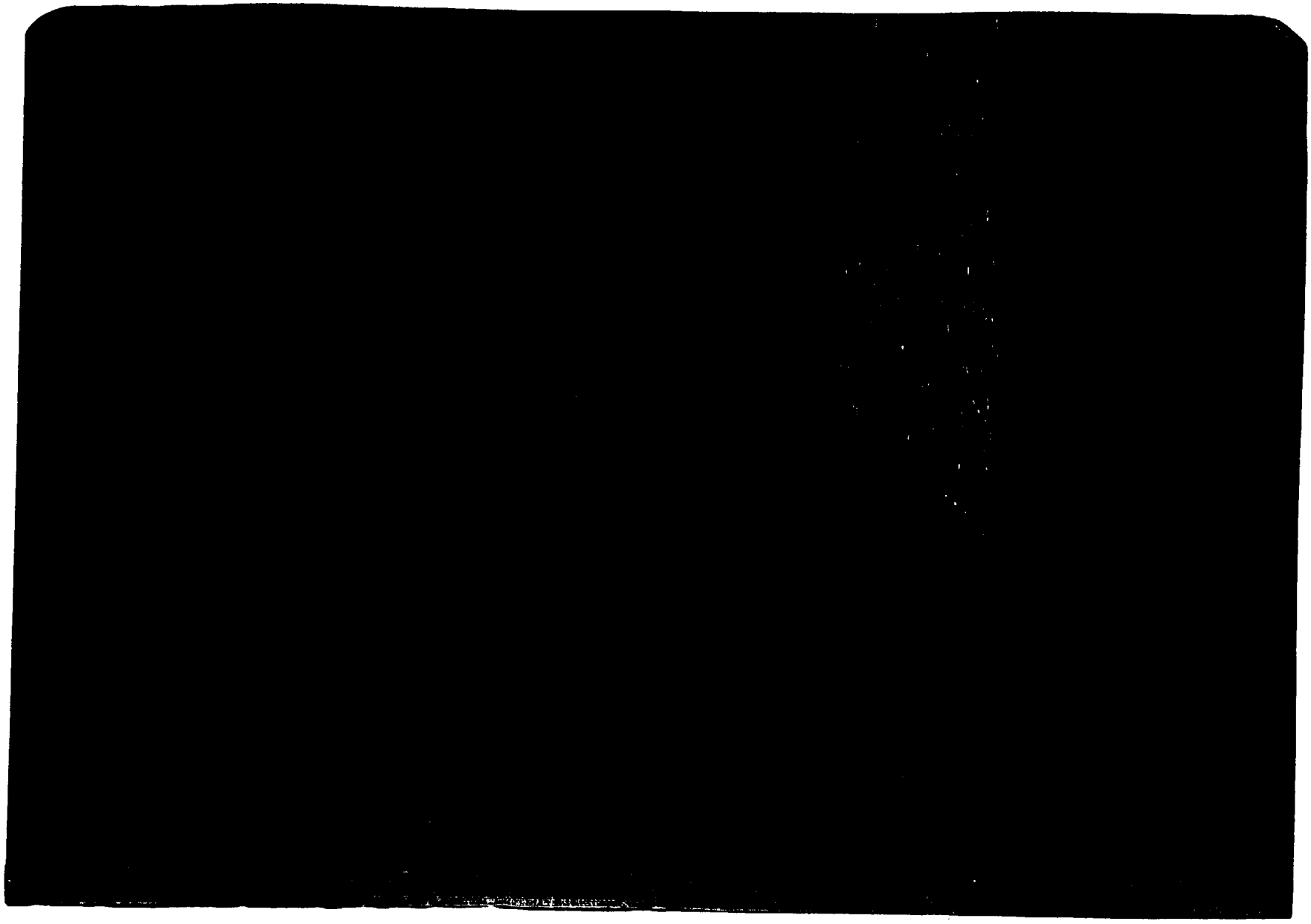

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